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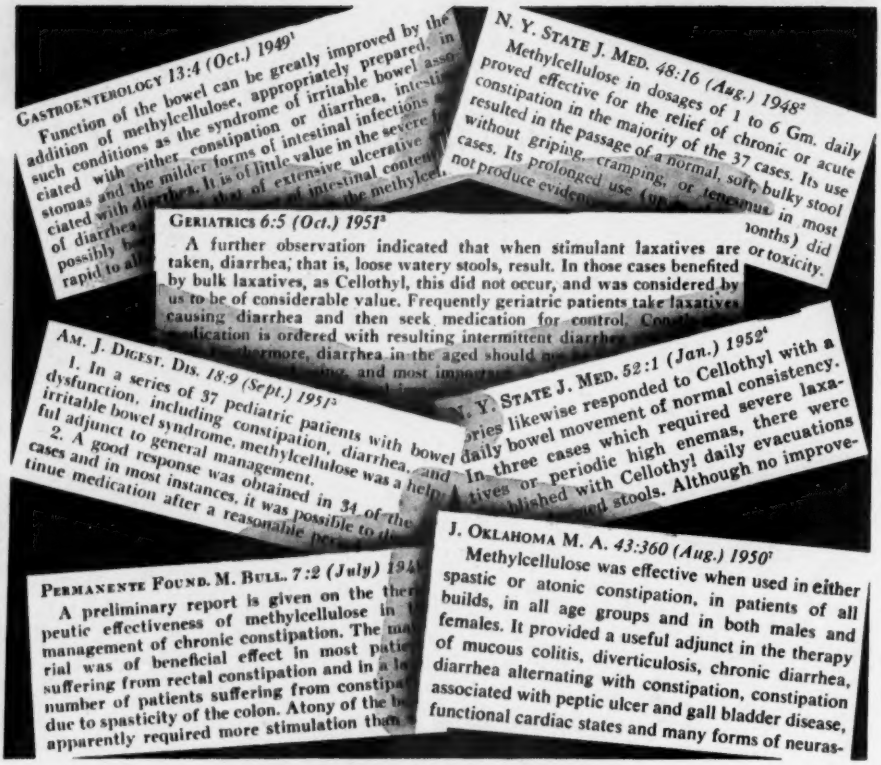
GASTROENTEROLOGY 13:4 (Oct.) 1949[1]
Function of the bowel can be greatly improved by the addition of methylcellulose, appropriately prepared, in such conditions as the syndrome of irritable bowel associated with either constipation or diarrhea, intestinal stomas and the milder forms of intestinal infections associated with diarrhea. It is of little value in the severe forms of diarrhea, that of extensive ulcerative possibly by rapid to al
N. Y. STATE J. MED. 48:16 (Aug.) 1948[2]
Methylcellulose in dosages of 1 to 6 Gm. daily proved effective for the relief of chronic or acute constipation in the majority of the 37 cases. Its use resulted in the passage of a normal, soft, bulky stool without griping, cramping, or tenesmus in most cases. Its prolonged use (up months) did not produce evidence or toxicity.
GERIATRICS 6:5 (Oct.) 1951[3]
A further observation indicated that when stimulant laxatives are taken, diarrhea, that is, loose watery stools, result. In those cases benefited by bulk laxatives, as Cellothyl, this did not occur, and was considered by us to be of considerable value. Frequently geriatric patients take laxatives causing diarrhea and then seek medication for control. Constipation is ordered with resulting intermittent diarrhea.
AM. J. DIGEST. DIS. 18:9 (Sept.) 1951[5]
1. In a series of 37 pediatric patients with bowel dysfunction, including constipation, diarrhea, and irritable bowel syndrome, methylcellulose was a helpful adjunct to general management.
2. A good response was obtained in 34 of the cases and in most instances, it was possible to discontinue medication after a reasonable
N. Y. STATE J. MED. 52:1 (Jan.) 1952[4]
...ries likewise responded to Cellothyl with a daily bowel movement of normal consistency. In three cases which required severe laxatives or periodic high enemas, there were ...blished with Cellothyl daily evacuations ...ed stools. Although no improve-
PERMANENTE FOUND. M. BULL. 7:2 (July) 194
A preliminary report is given on the therapeutic effectiveness of methylcellulose in the management of chronic constipation. The material was of beneficial effect in most patients suffering from rectal constipation and in a large number of patients suffering from constipation due to spasticity of the colon. Atony of the bowel apparently required more stimulation than
J. OKLAHOMA M. A. 43:360 (Aug.) 1950[7]
Methylcellulose was effective when used in either spastic or atonic constipation, in patients of all builds, in all age groups and in both males and females. It provided a useful adjunct in the therapy of mucous colitis, diverticulosis, chronic diarrhea, diarrhea alternating with constipation, constipation associated with peptic ulcer and gall bladder disease, functional cardiac states and many forms of neuras-

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Bibliography: 1. Bargen, J. A. 2. Schweig, K. 3. Wechsler, L.; Kessler, L. A., and Goldsmith, M. F. 4. Keeler, K. C., and Rusk, H. A. 5. Seidmon, E. E. P. 6. Newey, J. A., and Goetzl, F. R. 7. Musick, V. H.

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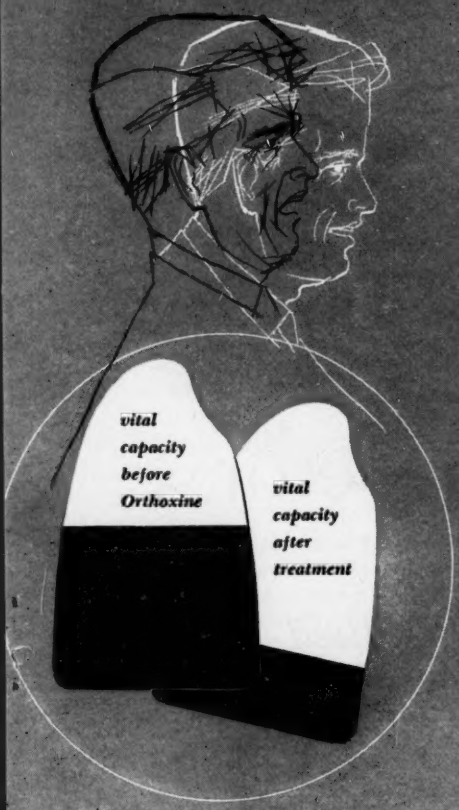

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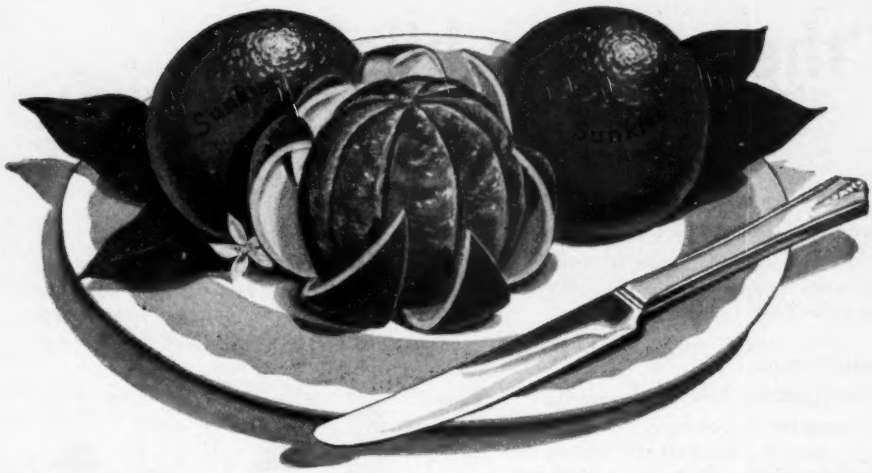
Eating whole oranges daily can have far-reaching effects on nutritional health and general well-being, accomplished through the promotion of improved intestinal function, a better intestinal environment, and enhanced nutrient absorption.



The beneficial effects of the protopectins begin with the release of pectin into the intestinal contents. Here is what you may look for from the daily ingestion of protopectins as supplied by California oranges, when the fruit —properly peeled—is eaten whole:

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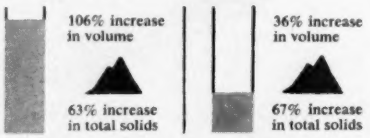

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VOLUME 89 JUNE 1952 NUMBER 6

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Editorials

THE SPREAD OF VIRUSES TO SUSCEPTIBLE HOSTS

DURING January, February, and March, 1951, an outbreak of severe encephalitis occurred in Australia. It was confined almost completely to the region drained by the Murray River and its tributaries and for that reason was soon designated Murray Valley encephalitis. In its clinical aspects it was very similar to "Australian X disease," which was described as occurring in a wider area including the Murray Valley in 1917 and 1918 but which disappeared thereafter except for a few sporadic cases in 1922 and 1925.[1] Intensive efforts by private practitioners, public health investigators, and veterinarians during the past year have established the fact that a specific virus is the cause of Murray Valley encephalitis.[2] In addition to finding antibodies in significantly high titers in about 25 per cent of the population in the endemic areas, antibodies have been found in horses and a variety of wild and domesticated fowl in the disease area.[3] The available evidence points to these birds as the important reservoir of the virus, with mosquitoes acting as the vectors in transmitting the disease to human beings.

Clinically the disease has characteristics in common with Japanese B, St. Louis, and eastern and western equine encephalitis in the United States.[4] In vitro serologic tests [2] indicate the virus to be closely related to but distinct from that of Japanese B encephalitis. It is now under study by Col. J. E. Smadel, of the Army Medical Center, Washington, D. C., but no reports on its serologic relationship to the other arthropod-borne neurotropic viruses have yet appeared.

The promptness with which the virus of Murray Valley encephalitis has been identified and the natural history of the disease established are in sharp contrast to the unsuccessful efforts to unravel the mysteries surrounding the spread of poliomyelitis

1. Anderson, S. G.: Murray Valley Encephalitis: Epidemiological Aspects, M. J. Australia **1**:98 (Jan. 26) 1952.

2. French, E. L.: Murray Valley Encephalitis: Isolation and Characterization of the Etiological Agents, M. J. Australia **1**:100 (Jan. 26) 1952.

3. Anderson, S. G.; Donnelley, M.; Stevenson, W. J.; Caldwell, N. J., and Eagle, M.: Murray Valley Encephalitis: Surveys of Human and Animal Sera, M. J. Australia **1**:110 (Jan. 26) 1952.

4. Robertson, E. G., and McLorinan, H.: Murray Valley Encephalitis: Clinical Aspects, M. J. Australia **1**:103 (Jan. 26) 1952. Robertson, E. G.: Murray Valley Encephalitis: Pathological Aspects, ibid. **1**:107 (Jan. 26) 1952.

—another disease almost certainly caused by a neurotropic virus. An informative analysis of the problem has recently been presented by Dr. F. M. Burnet, of the University of Melbourne.[5]

Until a few years ago the gastrointestinal tract was never considered to be the natural habitat of any virus. Now overwhelming evidence indicates that at least three poliomyelitis viruses, ten Coxsackie-type viruses, and the virus of infectious hepatitis grow abundantly in the gastrointestinal tract. Most investigators believe that poliomyelitis is spread from person to person by transfer of infected feces through contaminated water or food. In a community in which there is an epidemic probably a majority of the people ingest the virus, yet in only a very small proportion of the population—probably less than one-tenth of one per cent in most communities —does localization of the virus in the anterior horn cells of the spinal cord or brain stem occur in sufficient concentration to produce paralytic poliomyelitis. Factors determining such localization are the inherent invasiveness of the strain concerned and the presence or absence in the host of antibodies produced by previous subclinical attacks with the same strain. Another factor is the age of the person infected. In communities in which a given outbreak has, so far as one can learn, been the first to have ever occurred and the whole population is thus considered to be nonimmune, the lowest attack rate is in infants and the highest in adolescents and young adults. The reason for greater susceptibility at these ages is not well understood, but this important observation has been made in such virgin-soil outbreaks as those in St. Helena, Guam, New Guinea, the Solomon Islands, and the Eskimo villages of the Canadian Arctic. Experimentally the production of immunity by subclinical attacks has been demonstrated in chimpanzees in two ways. A previously uninfected animal is fed the virus, and daily tests are made on the feces. In two to four days the virus appears in the feces and persists for two to three weeks. A second feeding of the same virus months later is followed by virus excretion in the feces for only a day or two, representing presumably only the inoculum fed, there being no multiplication within the gastrointestinal tract. The second proof is the appearance of virus-neutralizing antibodies in the blood of the animals inoculated. This abundant antibody presumably diminishes the chances of ingested viruses being transferred to the central nervous system of immune animals.

In the island of Malta in which poliomyelitis was known to have occurred in previous years, there was another outbreak. The greatest incidence of disease in this outbreak was in children under 5 years of age—the ones presumably not immunized by subclinical attacks in previous epidemics—with relatively few infections of persons older than this. In the first outbreak on St. Helena—a virgin-soil area—the incidence in young children was practically the same as that on Malta, but by far the greatest number of cases was in the 5- to 20-year age group, which had a minimal attack rate in Malta. Such observations can be explained only by assuming that subclinical attacks produce an immunity that protects against the paralytic form of the disease in later years.

Such facts as have been reviewed are of extreme importance and mark a great advance over the scanty knowledge of the natural history of poliomyelitis which

5. Burnet, F. M.: Poliomyelitis and Murray Valley Encephalitis: A Comparison of Two Neurotropic Virus Diseases, M. J. Australia **1**:169 (Feb. 9) 1952.

was available even a decade ago. However, the almost explosive outbreak of simultaneous cases in widely scattered communities and widely separated homes within these communities has not yet been explained. Also, even though sewage has been found to contain the virus in appreciable amounts in communities in which there is a poliomyelitis outbreak, the means of pollution of pure water supplies and food has not been demonstrated. There is some evidence that flies may carry the inoculum, but other insects and other factors yet undiscovered undoubtedly play a role.

The seasonal incidence of the disease, which in temperate climates begins in early summer and reaches its maximum in virulence and number of cases in late summer and early fall, then subsides abruptly after the first frost, has also not been satisfactorily explained. Such a seasonal performance is compatible with the idea that flies and other insects may be concerned in its spread. The means by which the virus is preserved through the cold weather is not established.

In this connection a recent account of the spread of viruses from infected to susceptible hosts in certain diseases of animals by Dr. Richard E. Shope, of the Rockefeller Institute, is of great interest.[6] In his studies he was particularly interested in the origin of the virus responsible for the "first cases" in an epidemic. He points out that diseases considered highly contagious often are not contagious in the sense of direct spread of disease from one animal to another. They merely appear to be so. A large number of cases of illness appear almost simultaneously because they are acquired at the same time from the same reservoir. The reservoir may be another animal species, and insects or helminths may be the vectors.

An example is swine influenza, which begins abruptly late in October or early November. Farms isolated from each other but in the same general area are struck by the disease with such rapidity that the conclusion is almost inescapable that some agent already present on the various farms is responsible for the outbreaks rather than that the contagion is spread from one farm to another. By late December the epidemic has usually run its course.

Years of painstaking study have led Shope and his associates to the conclusion that swine influenza is caused not by a single micro-organism but by a bacterium, Hemophilus influenzae suis, and a specific virus working in concert. The bacterial component of the paired agents can persist indefinitely in the upper respiratory tracts of recovered swine; thus, it is readily present for the inoculation of nonimmune animals. The persistence of the virus after recovery cannot be demonstrated. However, Shope found that other swine could be carriers of "masked" virus which could, by certain manipulation, be provoked to infectivity. This masked virus was found to be acquired through an intermediate host, the swine lungworm. However, the lungworm has an intermediate host of its own, the common earthworm. Three of the developmental stages of the lungworm are spent in the earthworm. Then when swine ingest the parasitized earthworms by rooting in the soil, they, in turn, become parasitized with the lungworms. If these lungworm larvae were hatched from eggs

6. Shope, R. E.: The Spread of Viruses from Infected to Susceptible Hosts, in The Pathogenesis and Pathology of Viral Diseases, ed. by J. G. Kidd, New York Academy of Medicine, Section on Microbiology, Symposia No. 3, New York, Columbia University Press, 1950.

laid by an adult lungworm while she was infesting the lung of a pig with influenza, they will be carriers of masked influenza virus. Swine harboring the virus may appear to be perfectly normal until some stimulus, which in itself may appear harmless, initiates the rapid spread of the infection in the pig. Experimentally several different stimuli have been effective, but the most constantly successful one was the intramuscular injection of H. influenzae suis. Shope believes that the natural stimulus in a herd harboring the two infectious agents whose symbiotic existence seems necessary to set the infection in motion is the onset of wet, cold, inclement weather.

It has been found that infected third-stage lungworm larvae can persist as long as 32 months in their earthworm intermediate hosts and at least three months in association with adult lungworms in the swine respiratory tract. Survival of the virus from one outbreak to another is thus easily explained.

An example of the strange behavior of viruses in the gastrointestinal tract which conceivably could be analogous to the mode of invasion in poliomyelitis is found in the incomparable studies of Pasteur on the diseases of silkworms.[7] The obvious disease which was spreading so rapidly in nurseries of southern France in 1865 that the industry was threatened with extinction was *pébrine,* manifested by the appearance in the tissues of the infected worms of tiny black spots like pepper. Undertaking the study of this strange disease in an era in which the mechanisms of the spread of contagious disease were not even remotely understood, Pasteur showed that the essential factor in the disease was the presence of minute corpuscles which were seen only under the microscope and were transferred through the eggs of the silkworm to the next generation. However, for two years, although insisting that the presence of these microscopic corpuscles always indicated disease and were the only way of diagnosing it with certainty, he believed that they were the result of the malady rather than the cause of it. His reasons for this contention were that

> . . . the feeding of mulberry leaves contaminated with corpuscular material, either in the form of dust from a silkworm nursery, or of ground-up moths or worms loaded with corpuscles, often kills the worms very rapidly without giving them the corpuscles. . . . I have not been able to discover a mode of reproduction of the corpuscles, and its manner of appearance makes it resemble a product of the transformation of the tissues of the worms.

Although these doubts seemed reasonable enough, they were invalidated by the recognition the following year that he was dealing with two diseases, the second one called *flacherie.* The latter, not requiring the presence of corpuscles, had apparently caused the death of the worms developing from noninfected eggs but fed with material inadvertently contaminated with *flacherie* inoculum. This disease was proved by Pasteur not to be caused by corpuscles deposited in the egg by an infected moth but by ingestion of contaminated excreta from other diseased worms. Worms feeding on bruised or fermenting mulberry leaves under hot, humid conditions succumbed most rapidly. Their intestinal contents were found to contain streptococci or anaerobic bacilli in great abundance but not always in association with each other or in any constant proportion. Recent information suggests that

7. Duclaux, E.: Pasteur: The History of a Mind, Philadelphia, W. B. Saunders Company, 1920, pp. 145-178. Dubos, R. J.: Louis Pasteur, Free Lance of Science, Boston, Little, Brown & Company, 1950, pp. 209-233.

the primary cause of the condition is a filtrable virus causing a disease so mild that it escapes detection but renders the silkworms more susceptible to a variety of bacteria eaten along with mulberry leaves. Thus, the disease in its final form does not occur until a certain set of conditions makes possible the growth of the virus and bacteria simultaneously in an already weakened organism. The hygienic and meteorologic factors which favor the growth of the virulent bacteria in the environment of silkworms are necessary for producing the final fatal outcome.

Could it be that the presence of a particularly favorable bacterial flora, both quantitatively and qualitatively, in the gastrointestinal tracts of susceptible young persons in the late summer months is an important factor in raising the invasiveness of the poliomyelitis virus to the level necessary for its successful attack on the central nervous system?

All these questions are strictly within the realm of speculation. The patterns of virus dissemination cited in the above examples—only a few taken from many which are common knowledge—show the mysterious ways of both the visible and the invisible micro-organisms. By painstaking effort they can be discovered. The mystery of the poliomyelitis virus may be nearer solution than many of us think.

PAUL S. RHOADS, M.D.

MODERN CONCEPTS OF ACID-BASE REGULATION

ROBERT F. PITTS, Ph.D., M.D.
NEW YORK

ABOUT 100 years ago Claude Bernard pointed out that the true environment of the body is the interstitial fluid which circulates slowly through the tissue interstices, bringing to the cells their nutriments and removing from them their wastes.[1] This fluid is somewhat akin in composition to dilute sea water, having in common with it a balanced salt composition and a blandly alkaline reaction. Indeed it is probable that it mirrors the composition of the sea at that time in the prehistoric past when our Cambrian ancestors first found it advantageous to enclose a bit of the sea within their integument and to make it an intimate part of themselves.[2]

This interstitial fluid, like sea water, contains sodium bicarbonate and dissolved carbon dioxide or carbonic acid. These two components, one basic and one acidic, constitute a buffer mixture. Together they stabilize the reaction or hydrogen ion concentration of the fluid within a range favorable for vital cell activities.

The enclosure of a limited volume of interstitial fluid within an integument necessitated the development of homeostatic mechanisms for stabilizing its composition. Two such mechanisms are responsible for establishing and maintaining the blandly alkaline character of the body fluids. The respiratory system is charged with the responsibility for preserving constancy of carbonic acid concentration within limits of 1.2 and 1.4 mM. per liter. The kidneys are charged with the responsibility for preserving constancy of bicarbonate concentration within limits of 25 and 27 mM. per liter. Were either mechanism to fail, the resulting alteration in reaction of the internal fluid environment would so interfere with vital cell activities that continued function and even existence of the individual would be compromised.

It is my purpose to discuss briefly one aspect of the problem of homeostasis of body fluid reaction, namely, the mode of action of those renal mechanisms which preserve constancy of bicarbonate concentration of the plasma and interstitial fluid.

DUAL NATURE OF RENAL REGULATORY PROCESSES

The renal problem of maintaining the concentration of bicarbonate in the body fluids within normal limits is a dual one. The first aspect of the problem is that

---

Professor of Physiology, Cornell University Medical College.

Work mentioned as originating within my laboratory was supported by the National Heart Institute of the National Institutes of Health.

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1. Bernard, C.: Leçons sur les phénomènes de la vie commune aux animaux et aux végétaux, Paris, J. B. Ballière et fils, 1878.

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of the salvaging of the large quantities of bicarbonate which enter the renal tubules in the glomerular filtrate.[3] The efficiency with which this problem has been solved is indicated in the following considerations. Some 200 liters of plasma is filtered through the glomeruli of normal man each day. Since each liter contains roughly 25 mM. of bicarbonate, a total of 5,000 mM., or about 1 lb. (454 gm.) when expressed as sodium bicarbonate, is delivered into the tubules every 24 hours. This is five times the amount of bicarbonate which the body actually contains. Obviously, this salt must be filtered over and over again and reabsorbed each time by the renal tubules. The efficiency of the reabsorptive process is indicated by the fact that only 1 or 2 mM. escapes in the urine each day. However, if sodium bicarbonate is ingested or if the diet is such that it yields an alkaline ash residue, the excess bicarbonate is rapidly excreted in the urine.

The second aspect of the problem of the renal stabilization of the concentration of bicarbonate derives from the fact that nonvolatile acids, such as sulfuric and phosphoric acids, are formed in considerable quantities in the metabolism of phospholipids and proteins. These acids, neutralized in the body by base contributed by bicarbonate, tend to deplete body stores. This depletion would proceed at such a rate as to exhaust the bicarbonate reserves completely within a week were it not for two renal compensatory processes, namely, the excretion of titratable acid and the excretion of ammonia.[4]

In essence these two mechanisms reverse the process of neutralization, promote the elimination of acid anions minus the base which they bind in the blood, and restore that base to the body as bicarbonate.[5] In the excretion of titratable acid, neutral salts of weak buffer acids which enter the renal tubules in the glomerular filtrate are transformed into acid salts or even into free acids. The base is restored to the body as bicarbonate. In the example below, disodium phosphate is shown as reacting with carbonic acid to form sodium bicarbonate and monosodium phosphate.

$$Na_2HPO_4 + H_2CO_3 \rightarrow NaH_2PO_4 \text{ (excreted)} + NaHCO_3 \text{ (absorbed)}$$

The reaction is driven to the right by the reabsorption of sodium bicarbonate. The original filtrate, which like the plasma has a slightly alkaline reaction of pH 7.4, is thereby converted into urine as acid as pH 4.5. The base salvaged in this way by the average person amounts to 10 to 30 mEq. per day. Expressed in more conventional terms, the normal person excretes some 100 to 300 cc. of 0.1 N titratable buffer acid. This acid is largely monobasic phosphate.

The kidney can excrete negligible quantities of free hydrochloric or sulfuric acid, for the most acid urine which it can elaborate has a pH of 4.5. These strong acids must be eliminated fully neutralized, but the kidney accomplishes this end without sacrifice of sodium ions by combining them with ammonium ions. In the example below, sodium sulfate, delivered into the tubules in the filtrate, is shown as reacting with ammonium bicarbonate to produce sodium bicarbonate and ammonium sulfate.

$$Na_2SO_4 + 2\,NH_4HCO_3 \rightarrow (NH_4)_2SO_4 \text{ (excreted)} + 2\,NaHCO_3 \text{ (absorbed)}$$

3. Pitts, R. F.; Ayer, J. L., and Schiess, W. A.: The Renal Regulation of Acid-Base Balance in Man: III. The Reabsorption and Excretion of Bicarbonate, J. Clin. Invest. **28**:35, 1949.

4. Pitts, R. F.: (*a*) Renal Excretion of Acid, Federation Proc. **7**:418, 1948; (*b*) Acid-Base Regulation by the Kidneys, Am. J. Med. **9**:356, 1950.

5. Henderson, L. J.: A Critical Study of the Process of Acid Excretion, J. Biol. Chem. **9**:403, 1911.

Again the reaction is driven to the right by the reabsorption of sodium bicarbonate. The base salvaged in this way by the average person amounts to 30 to 50 mEq. per day, or, in more conventional terms, he excretes 300 to 500 cc. of 0.1 N acid per day neutralized with ammonia.

The sum of the titratable acid and ammonia eliminated is a measure of the total renal defense of the bicarbonate reserves.[6] If the acid load of the body is greatly increased and bicarbonate reserves are depleted, as is true in diabetic ketosis, the kidney can increase its output of titratable acid and ammonia by as much as 1,000%.[7]

So far I have defined the role of the kidneys in acid-base regulation as essentially one of stabilizing the concentration of bicarbonate in the plasma and interstitial fluid at a level of 25 to 27 mEq. per liter. I have pointed out that the renal tubules face a dual problem; first, the salvage of the large quantities of bicarbonate which are delivered into the tubules in the glomerular filtrate; second, the abstraction from the filtrate of the base which has been utilized in the body in neutralizing metabolic acids. I shall next consider the means by which the renal tubules under normal conditions solve these problems so effectively.

RENAL THRESHOLD RELATIONSHIP FOR BICARBONATE

The urine of the normal person maintained on an average mixed diet is slightly acid, the reaction averaging pH 6.0.[8] The urine contains negligible traces of bicarbonate. However, the ingestion of as little as 4 gm. of sodium bicarbonate ordinarily causes the urine to become slightly alkaline, and even large quantities of base may be readily eliminated in urine but slightly more alkaline than blood plasma. In fact, the most alkaline urine which the kidney can elaborate is pH 8.0.[9]

The relationship between blood plasma concentration and tubular reabsorption and excretion of bicarbonate in three normal adult subjects is illustrated in Figure 1.[3] The plasma level of bicarbonate was varied over a range extending from 13 to 38 mM. per liter in these experiments. The low values were obtained by ingestion of 10 to 15 gm. of ammonium chloride on the day preceding an experiment. Ammonium chloride is, of course, converted in the liver to urea and hydrochloric acid. The hydrochloric acid is immediately neutralized by sodium bicarbonate. The larger the dose of ammonium chloride, the greater is the depletion of body bicarbonate stores. In my study the plasma level was then gradually elevated by administering an intravenous infusion of sodium bicarbonate. Measurements of filtration, absorption, and excretion of bicarbonate were made at intervals as the plasma concentration was raised from subnormal, through normal, to elevated levels.

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6. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, Vol. 1: Interpretations.

7. Stillman, E.; Van Slyke, D. D.; Cullen, G. E., and Fitz, R.: Studies on Acidosis: VI. The Blood, Urine and Alveolar Air in Diabetic Acidosis, J. Biol. Chem. **30**:405, 1917.

8. Henderson, L. J., and Palmer, W. W.: On the Intensity of Urinary Acidity in Normal and Pathological Conditions, J. Biol. Chem. **13**:393, 1913.

9. Gamble, J. L.: Carbonic Acid and Bicarbonate in Urine, J. Biol. Chem. **51**:295, 1922. Marshall, E. K., Jr.: The Effect of Loss of Carbon Dioxide on the Hydrogen Ion Concentration of Urine, ibid. **51**:3, 1922.

In essence, this figure defines the renal threshold relationships for bicarbonate in normal man. At plasma concentrations ranging from 13 to 24 mEq. per liter, indicative of slight to moderately severe ammonium chloride acidosis, all the bicarbonate entering the glomerular filtrate is reabsorbed. None is allowed to escape in the urine. At plasma concentrations above 28 mEq. per liter absorption is less complete. In fact, from each 100 cc. of filtrate 2.8 mEq. is absorbed; all in excess of this amount is excreted. The renal plasma threshold for bicarbonate, therefore, lies between 25 and 27 mEq. per liter.

The significant fact about this absorptive process is how nicely it is poised to stabilize the plasma bicarbonate concentration at 25 to 27 mEq. per liter. If body stores of bicarbonate are normal or reduced, the filtered bicarbonate is entirely absorbed. Such a state of affairs is the usual one, for man ordinarily does not

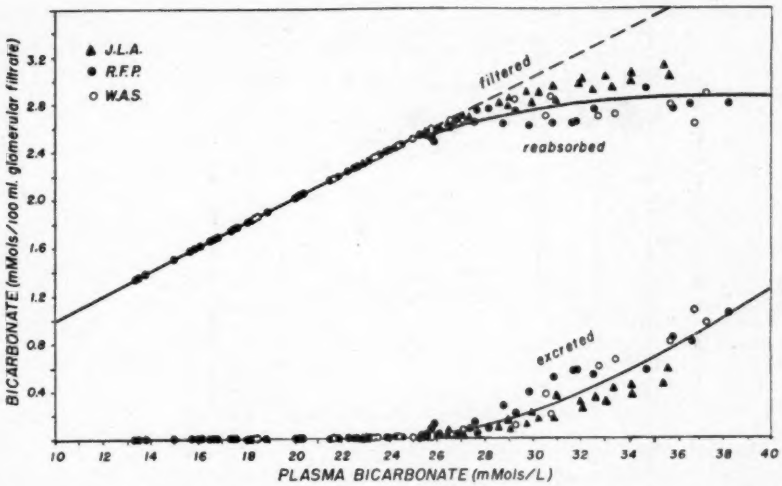

Fig. 1.—Reabsorption and excretion of bicarbonate in three normal adults as a function of plasma concentration. (From Pitts, Ayer, and Schiess.[3])

have any excess of base at his disposal. However, if sodium bicarbonate is administered, the plasma concentration rises above the normal range. All present in the plasma in excess of that amount which is optimal is excreted. The urine becomes alkaline because of its increased content of bicarbonate.

If there were no continued drain on man's bicarbonate stores to neutralize acids formed in fat and protein metabolism, or if he were to ingest each day an excess of sodium bicarbonate over and above that used in neutralizing these acids, the absorptive and excretory processes just described would serve to stabilize the plasma concentration of bicarbonate within the normal range. Man's independence of an exogenous supply of bicarbonate derives directly from an inherent renal capacity to manufacture his own supplies as needed. The kidney does this by excreting acid anions in free titratable form or in combination with ammonia and by salvaging the base with which they were neutralized in the body fluids.

EXCRETION OF TITRATABLE ACID

I shall consider first the mechanism for the excretion of titratable acid, namely, that mechanism which transforms the slightly alkaline blood plasma into acid urine. The studies of Montgomery and Pierce [10] on the amphibian kidney provide a morphological basis for an understanding of this process. These investigators withdrew minute quantities of fluid from the glomerulus and from the proximal, intermediate, and distal segments of the nephron and determined the pH with a microquinhydrone electrode. Figure 2, taken from their work, compares the reaction of the fluid obtained at each level with that of the plasma from which it was formed. It is evident that within reasonable limits the pH of the glomerular filtrate and the tubular fluid obtained from the proximal and intermediate segments is identical with that of the plasma. In the distal tubule the urine becomes

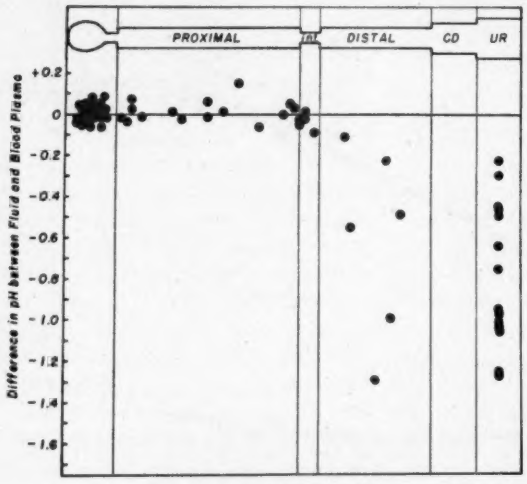

Fig. 2.—Comparison of pH of tubular fluid withdrawn at various levels from the amphibian nephron with pH of blood plasma. *INT* means intermediate segment of nephron; *CD*, carbon dioxide, and *UR*, urine. (From Montgomery and Pierce.[10])

acid, the pH decreasing to values as low as those observed in urine obtained from the ureter and bladder. Acidification of the urine and excretion of titratable acid are thus functions of the distal segment of the renal tubule.

Evidence is fairly conclusive that the distal tubular mechanism accomplishes acidification of the urine by a process of ion exchange, rather than by direct secretion of acid.[4] Present concepts of the nature of this exchange mechanism are illustrated in Figure 3. A single cell from that part of the distal tubule which is concerned with acidification of the urine is represented here in schematic form. Such a cell is exposed on one side to the tubular blood, on the other to the tubular urine. By virtue of its own metabolic activities, as well as its exposure to the

10. Montgomery, H., and Pierce, J. A.: The Site of Acidification of the Urine Within the Renal Tubule in Amphibia, Am. J. Physiol. **118**:144, 1937.

renal capillary blood, a continuous supply of carbon dioxide is available to it. Because of its high content of carbonic anhydrase, the cell can rapidly transform this dissolved gas into carbonic acid. Hydrogen ions dissociated from carbonic acid are exchanged across the luminal border of the cell for sodium ions in the tubular urine. The sodium, along with an equivalent quantity of bicarbonate, is returned to the renal venous blood. The hydrogen ions, along with the anion residue, are excreted in the urine as titratable acid.

The capacity of the kidney to salvage base in this manner is limited by both the nature and the quantities of the buffer salts present in the tubular urine at the site of acidification.[11] The kidney can operate most efficiently on weak acid buffers, such as phosphate. It can operate fairly well on medium acid buffers such as beta-hydroxybutyrate and acetoacetate. However, if it is to salvage any appreciable quantity of base from sodium chloride or sodium sulfate, the very strong acids formed, namely, hydrochloric and sulfuric acids, must be immediately neutralized with ammonia.

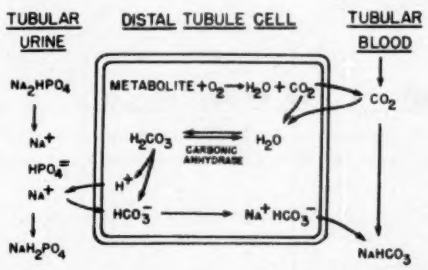

Fig. 3.—Schematic representation of cellular mechanisms concerned with acidification of urine. A single cell from distal segment of nephron is depicted. (From Pitts.[4a])

EXCRETION OF AMMONIA

To Nash and Benedict [12] belongs the credit for first demonstrating that the renal tubular cells form ammonia from some precursor in the arterial blood and secrete it in high concentration into the tubular urine. In Figure 4 are summarized experiments of Walker [13] which show that the secretion of ammonia, like the elaboration of acid urine, is a function of the distal tubule. Fluid drawn from the glomerulus and proximal tubule of the amphibian kidney contains only insignificant traces of ammonia. As fluid traverses the distal segment, ammonia is added in increasing amounts.

In the past, urea has been considered the most likely precursor of urinary ammonia, but Krebs, Van Slyke, and others have recently demonstrated that

11. Schiess, W. A.; Ayer, J. L.; Lotspeich, W. D., and Pitts, R. F.: The Renal Regulation of Acid-Base Balance in Man: II. Factors Affecting the Excretion of Titratable Acid by the Normal Human Subject, J. Clin. Invest. **27**:57, 1948.

12. Nash, T. P., Jr., and Benedict, S. R.: The Ammonia Content of the Blood and Its Bearing on the Mechanism of Acid Neutralization in the Animal Organism, J. Biol. Chem. **48**:463, 1921.

13. Walker, A. M.: Ammonia Formation in the Amphibian Kidney, Am. J. Physiol. **131**:187, 1940.

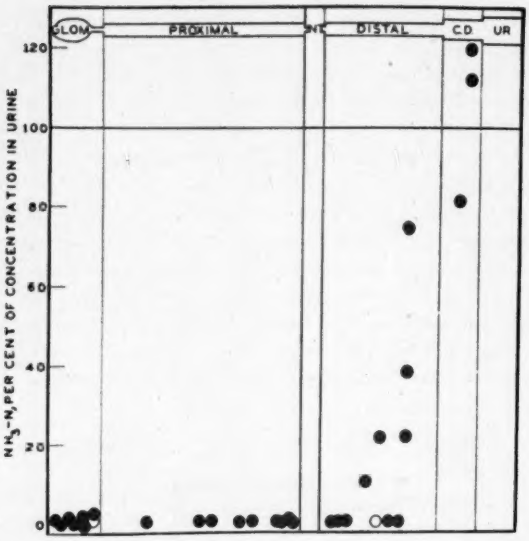

Fig. 4.—Concentration of ammonia in tubular fluid withdrawn at various levels from the amphibian nephron. See legend to Figure 2 for explanation of abbreviations. (From Walker.[18])

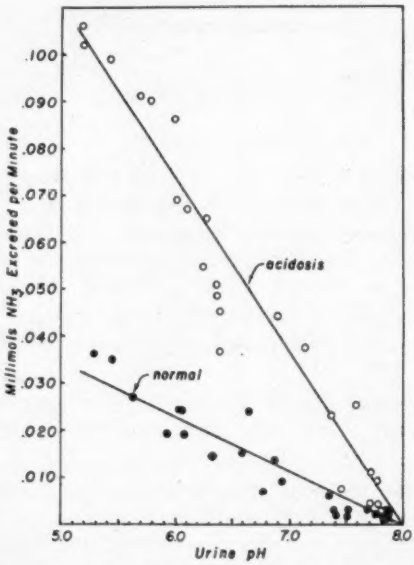

Fig. 5.—Comparison of relationship between rate of ammonia excretion and urine pH in normal and acidotic dogs. All data were obtained on one dog. Urine pH in each instance was elevated by infusion of sodium bicarbonate. (From Pitts.[4a])

glutamine and other amino acids are the true precursors and that no urea is converted to ammonia.[14]

It is now well recognized that the rate of ammonia excretion is proportional to the hydrogen ion concentration of the urine. The more acid the urine, the greater is the rate of ammonia excretion. The more alkaline the urine, the lower is its rate of excretion. The data presented in Figure 5 illustrate this fact well.[48]

All data on this chart were obtained in experiments on one dog. In each experiment sodium bicarbonate was infused to raise the plasma level until it exceeded the renal threshold. As increasing quantities of bicarbonate appeared in the urine, the pH of the urine increased. The series of data designated normal were obtained under normal conditions. In the series designated acidosis, ammonium chloride had been administered at intervals over the preceding 48 hours to induce a moderately

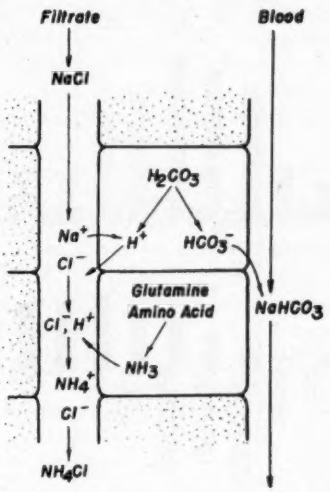

Fig. 6.—Schematic representation of origin of relationship between rate of ammonia excretion and urine pH. Two processes of hydrogen ion exchange and of ammonia formation occur within same segment of renal tubule, probably within same cells of that segment. (From Pitts [48].)

severe acidosis. In either condition, the relationship between rate of ammonia excretion and urine pH is evident. Obviously some adaptation had occurred during the two-day period of acidosis which increased the animal's capacity to excrete ammonia at any given urine pH. This adaptation is at least in part a function of adrenal cortical stimulation, but space does not justify its further consideration.

Two known facts indicate that the renal mechanism for ammonia excretion is closely related functionally to that for titratable acid excretion. First, ammonia excretion, like titratable acid excretion, mole for mole restores base to the body as bicarbonate. Second, the rate of ammonia excretion is inversely related to urine

14. Krebs, H. A.: Untersuchungen über den Stoffwechsel der Aminosäuren im Tierkörper, Ztschr. physiol. Chem. **217**:191, 1933. Van Slyke, D. D.; Phillips, R. A.; Hamilton, P. B.; Archilbald, R. M.; Futcher, P. H., and Hiller, A.: Glutamine as a Source Material of Urinary Ammonia, J. Biol. Chem. **150**:481, 1943.

pH and hence must in some way be dependent on the mechanisms of titratable acid excretion.[4] My views of the nature of the interrelationships of the two mechanisms are outlined in Figure 6. If the tubular urine contained only salts of strong acids, such as sodium chloride, the exchange of hydrogen ions for sodium ions could occur to a very limited extent, for the hydrochloric acid formed is highly dissociated. The high concentration of hydrogen ion attained in the urine would block appreciable transfer. The secretion of ammonia into the urine neutralizes this acid by binding the hydrogen ions as ammonium ions, thereby permitting the continued exchange of hydrogen ions for base. Each molecule of ammonia secreted into the urine binds one hydrogen ion and permits one sodium ion to be absorbed. Thus, ammonia is exchanged for base mole for mole, although the exchange is

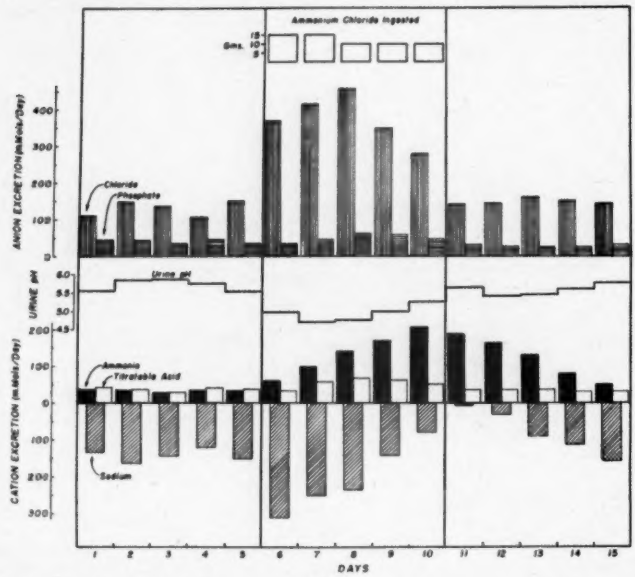

Fig. 7.—Renal excretion of ions by a subject with normal renal function prior to, during, and following imposition of an acid load in form of ammonium chloride given by mouth. (From Sartorius, Roemmelt, and Pitts.[15])

indirect. The factor of urine pH no doubt plays its role by determining the rate of diffusion of free ammonia across the luminal border of the tubular cell.

RENAL RESPONSE TO ACIDOSIS IN NORMAL MAN

The means by which the normal person withstands the initial insult of a suddenly imposed acid load, and the way in which his kidneys repair the damage to the acid-base structure of his body fluids, are illustrated in Figure 7. For 15 days the subject was maintained on a diet constant with respect to calories, protein, and electrolyte.[15] Successive 24-hour urine samples were collected and analyzed for

15. Sartorius, O. W.; Roemmelt, J. C., and Pitts, R. F.: The Renal Regulation of Acid-Base Balance in Man: IV. The Nature of the Renal Compensations in Ammonium Chloride Acidosis, J. Clin. Invest. **28**:423, 1949.

selected ionic constituents. The rates of excretion of these several constituents, expressed in milliequivalents per day, are plotted in block form. During the first five days, which constitute the control phase of the experiment, the net load of acid produced in the metabolism of the dietary protein and fat averaged 79 mEq. per day, 35 mEq. of which was excreted in combination with ammonia and 44 mEq. as free titratable acid. The subject was in electrolyte balance, excreting on an average 140 mEq. of sodium, 130 mEq. of chloride, and 41 mM. of phosphate per day. In this chart the excretion of sodium is plotted downward from that of ammonia and titratable acid to emphasize its opposite relation to base economy.

The acid load on the body was increased sharply during the second five-day period by the ingestion of 10 to 15 gm. of ammonium chloride per day. Fifteen grams of ammonium chloride constitutes a load equivalent to 2,900 cc. of 0.1 N. hydrochloric acid.

It is evident that chloride excretion rose sharply on the first day of increased acid load. Urine pH dropped from a mean control level of 5.7 to 4.9, but, since little hydrochloric acid can exist free in urine of this reaction, and since ammonia excretion was only moderately increased, the excess chloride was almost entirely neutralized by sodium drawn from the buffer stores of the body.

During the subsequent four days of acid ingestion, this threat to the alkali reserve was met by the excretion of more titratable acid and, most significantly, by the excretion of increased quantities of ammonia. As ammonia excretion increased, base loss diminished in proportion, until on the last day of acid ingestion a positive sodium balance was attained. Recovery had thus begun, although the acid load was still great.

The processes of recovery and restoration of normal acid-base balance are well illustrated in the final five-day period of this experiment. On the first day of recovery essentially no sodium was excreted; all that ingested in the diet was retained in the body. Anions were largely eliminated in combination with ammonia, for the rate of excretion of ammonia was maintained near its peak level. Retention of sodium was evident for five days, during which time the excess loss in the period of acidosis was restored to the body in full. On the sixth day of recovery, which is not shown in this chart, all disturbances had been corrected completely and conditions were back to normal.

RENAL RESPONSE TO ACIDOSIS IN DIABETIC KETOSIS

An analogous experiment performed a number of years ago by Atchley, Loeb, Richards, Benedict, and Driscoll [16] on a young severely diabetic patient is illustrated in Figure 8. Their subject required 85 units of insulin per day for adequate control of his disease. Upon such a regimen, excretion of ketone bodies was essentially zero, and acid-base balance was attained during the control period by the elimination of 40 mEq. of acid in combination with ammonia and 30 mEq. in free titratable form, essentially the same quantities as in the previous normal subject. When insulin administration was discontinued for four days, an increasingly severe ketosis developed, illustrated in the upper part of the chart by a progressively increasing rate of excretion of beta-hydroxybutyric acid. This extra urinary acid was neutralized in part by the fixed bases, sodium, potassium, and calcium, and in

16. Atchley, D. W.; Loeb, R. F.; Richards, D. W., Jr.; Benedict, E. M., and Driscoll, M. E.: On Diabetic Acidosis: A Detailed Study of Electrolyte Balances Following the Withdrawal and Reestablishment of Insulin Therapy, J. Clin. Invest. **12**:297, 1933.

part by ammonia. A significant fraction was eliminated in free titratable form, for in urine of pH 5.3 roughly 30% of beta-hydroxybutyric acid can exist as free acid. Despite increased excretion of titratable acid and ammonia, a severe acidosis developed, and it was necessary to terminate the experiment by the institution of insulin therapy. As in the normal subject, the continued excretion of ammonia at a high rate permitted the restoration of base reserves and the attainment of equilibrium by the fifth day.

This experiment, and the previous one as well, illustrates the capacity of the normal kidney to correct disturbances of acid-base balance when provided with adequate quantities of fluid and sodium chloride. For such persons alkali therapy

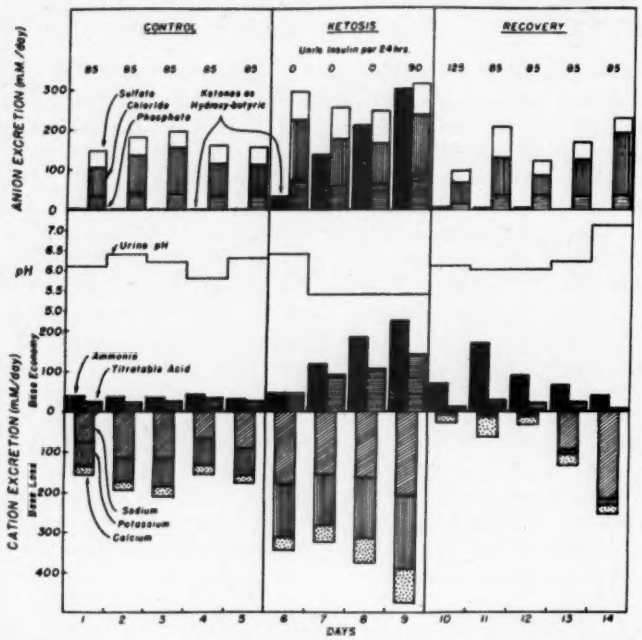

Fig. 8.—Renal excretion of ions by a diabetic subject with normal renal function prior to, during, and following development of ketosis as a result of temporary withdrawal of insulin administration. (Drawn from data of Atchley, Loeb, Richards, Benedict, and Driscoll.[16])

of acidosis is unnecessary. The young diabetic, his body adequately hydrated with saline and dextrose infusions and his disease controlled with insulin, can correct a severe ketosis promptly without risking alkalosis. Such is not necessarily the case in the elderly diabetic, who may exhibit relative or absolute renal insufficiency.

RENAL RESPONSE TO ACIDOSIS IN NEPHRITIS

In Figure 9, taken from the work of Gamble, Blackfan and Hamilton,[17] the response of a normal person to a standard acid load is compared with that of a

17. Gamble, J. L.; Blackfan, K. D., and Hamilton, B.: A Study of the Diuretic Action of Acid Producing Salts, J. Clin. Invest. **1**:359, 1925.

patient with chronic nephritis. Calcium chloride was administered as the acidifying agent. In each graph the urinary rates of excretion of chloride, fixed base, and ammonia are plotted as increments over foreperiod levels. It is evident in both the normal and the nephritic subjects that, early in the period of acid stress, the excess urinary chloride was largely neutralized by fixed base. However, in the normal subject ammonia excretion increased promptly and by the sixth day was of sufficient magnitude to cover the chloride load. Loss of fixed base ceased, and, in the succeeding recovery period, depleted base reserves were restored promptly. In contrast, ammonia excretion in the nephritic subject increased but little. Loss of fixed base continued at a high rate, and it was necessary to terminate the experiment

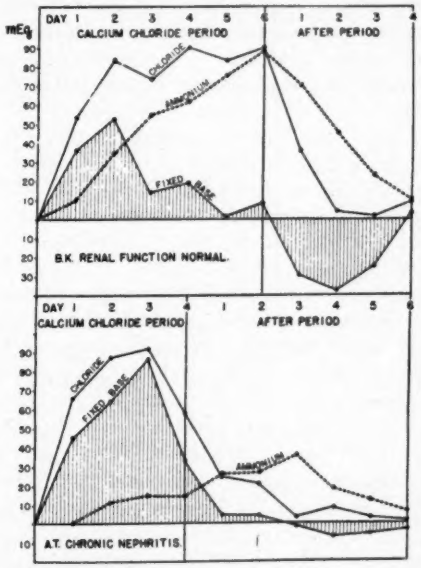

Fig. 9.—Comparison of renal excretion of ions by a subject with normal renal function and by a subject with chronic nephritis during and following imposition of an acid load in form of calcium chloride given by mouth. Rates of excretion of chloride, fixed base, and ammonia are plotted as increments over values established during control periods. (From Gamble, Blackfan, and Hamilton.[17])

on the fourth day because of the development of severe acidosis. Recovery was slow and inadequate.

SUMMARY

The kidney participates in the regulation of body neutrality by stabilizing the plasma concentration of bicarbonate at a level of 25 to 27 mEq. per liter.

The problem of stabilizing the concentration of bicarbonate is a dual one, involving both the salvage of the filtered bicarbonate and the restoration to the body of the base utilized in neutralizing metabolic acids. In a quantitative sense, salvage of bicarbonate from the glomerular filtrate is the more significant, for each day more than a pound of the sodium salt is absorbed by the renal tubules. The

efficiency of the absorptive mechanism is such that under normal conditions less than 1/10th of 1% of the bicarbonate filtered is wasted in the urine. Nevertheless, after the ingestion of bicarbonate, large quantities can be eliminated in the urine with only a slight increase in plasma level.

Although their daily ion turnover is considerably less, the mechanisms which substitute hydrogen or ammonium ions for sodium ions in the tubular urine play a role no less significant in the maintenance of acid-base balance than do those for absorption of bicarbonate. By virtue of these ion substitutions, metabolic acids may be excreted in free titratable form and in combination with ammonia without sacrifice of the limited stores of body base. It is evident that the acidosis of diabetic ketosis is a consequence of the flooding of the body with such a load of metabolic acid that the kidneys are unable to substitute ammonia and hydrogen ions rapidly enough to prevent depletion of base. The acidosis of chronic nephritis, on the other hand, results, at least in part, from the inability of the damaged tubules to effect these exchanges with sufficient rapidity to compensate for a normal load of metabolic acid.

SARCOID-LIKE GRANULOMATA OF THE PITUITARY GLAND

A Cause of Pituitary Insufficiency

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AND
STANLEY L. ROBBINS, M.D.
BOSTON

DESTRUCTION of the pituitary gland by giant-cell granulomata is a poorly understood, seldom recognized cause of pituitary insufficiency. While these granulomata are readily apparent pathologically, their cause is obscure. They have been considered to be sarcoid or tuberculosis.[1] A syphilitic causation has often been questioned.[2] Some have considered these lesions to be a distinct, specific disease of unknown origin.[3] It is probable that four etiological processes are involved in the reported cases of this disease. In the literature 16 cases have been associated with typical uveoparotid fever, osteitis multiplex cystica, lupus pernio, hyperglobulinemia, or other characteristics of Besnier-Boeck-Schaumann sarcoidosis. In some of these cases, furthermore, the asteroid and Schaumann bodies which are so suggestive of sarcoidosis have been demonstrated.[4] Occasional reported cases may represent a healed syphilitic process: In the case of Oelbaum and Wainwright the association of pituitary granulomata with the almost pathognomonic syphilitic lesions of interstitial keratitis and deformity of the teeth and with a granuloma of the testis seems more than coincidence.[2] Additional cases seem to represent a chronic or inactive, noncaseous, miliary tuberculosis localized to the pituitary and associated with a focus of caseous or acid-fast infection in some other organ or organs of the body. In 13 of the collected cases of cryptogenic pituitary granuloma there was systemic tuberculosis (Tables 1, 2, and 3). The case of Berblinger is unique, being truly one of only a granulomatous disease of the pituitary capsule. It may conceiv-

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1. (*a*) Kraus, E. J.: Sarcoidosis (Boeck-Besnier-Schaumann Disease) as Cause of Pituitary Syndrome, J. Lab. & Clin. Med. **28**:140-146, 1942. (*b*) Coleman, C. C., and Meredith, J. M.: Diffuse Tuberculosis of the Pituitary Gland Simulating Tumor, with Postoperative Recovery, Arch. Neurol. & Psychiat. **44**:1076-1085 (Nov.) 1940.

2. Oelbaum, M. H., and Wainwright, J.: Hypopituitarism in a Male Due to Giant Cell Granuloma of the Anterior Pituitary, J. Clin Path. **3**:122-129, 1950.

3. Sheehan, H. L., and Summers, V. K.: The Syndrome of Hypopituitarism, Quart. J. Med. **18**:319-378, 1949.

4. (*a*) Kraus.[1a] (*b*) Doniach, I., and Wright, E. A.: Two Cases of Giant-Cell Granuloma of the Pituitary Gland, J. Path. & Bact. **63**:69-79, 1951.

TABLE 1.—*Reported Cases of Giant-Cell Granulomata of the Pituitary with Hypopituitarism*

Case No.	Author; Year	Sex	Age	Loss of Sexual Function	Loss of Body Hair	Loss of Strength	B. M. R.	Clinical Comment	Cause of Death	Tuberculous or Syphilitic Lesions	Distribution of Granulomata	Author's Diagnosis
1	Gougerot and Gy,[8] 1911.....	M	52	+	+	+	.....	Transient polydipsia	Pneumonia	Lung apex	Pituitary "lupus" of nose; "fibrosis" of liver, spleen, pancreas	.....
2	Berblinger,[5] 1927	M	43	+	+	+	.....	Skull fracture 3 yr. before	?	.....	Pituitary	.....
3	Roessle (Case 2), 1934; cited by Sheehan and Summers [3].....	F	52	+	+	..	.....	Excessive thirst	.....	.....	Pituitary	.....
4	Boller and Goedel (Case 1): Wien. Arch. inn. Med. 27:41, 1935.....	F	51	+	+	+	−24%	Pallor	Cachexia; pneumonia	None	Pituitary	.....
5	Boller and Goedel (Case 2): Wien. Arch. inn. Med. 27:41, 1935.....	F	69	..	+	+	−24%	Multinodular thyroid	Hypopituitarism	Lung apex; hilar nodes	Pituitary	.....
6	Coleman and Meredith,[1b] 1940.....	F	57	..	..	..	−12%	Headache; loss of vision	Diagnosed by biopsy	.....	Pituitary	.....
7	Kirshbaum and Levy (Case 2): Arch. Int. Med. 68:1095, 1941.....	M	44	..	+	+	.....	Blindness; deafness	Hypopituitarism	Primary complex, right lower lobe	Pituitary	Tuberculosis
8	Kraus,[1a] 1942	F	41	+	+	..	.....	Polyuria	Hypopituitarism	? Lung apex	Pituitary; lungs; spleen; nodes; liver	Sarcoid
9	Terpestra,*[1c] 1944	..	41	+	..	+	.....	Hemianopsia; polydipsia; polyuria; oligosthenuria	Diagnosed by biopsies	Lungs, ? healed	? Pituitary; skin; nodes; tongue; lungs; parotid	Sarcoid
10	Barber,*[1d] 1945	..	28	+	+	+	.....	Transient polydipsia	Diagnosed clinically	? Hilar nodes	? pituitary; eyes; bones; skin; nodes	Sarcoid
11	Herlant (Case 1): Acta clin. belg. 1:197, 1946	F	66	..	?	..	−9%	.....	Hypoglycemia	.....	Pituitary	Nonspecific giant-cell granuloma
12	Herlant (Case 2): Acta clin. belg. 1:197, 1946	F	62	+	+	+	.....	Pallor	Coma	.....	Pituitary	Atrophy
13	Sheehan and Summers,[3] 1949.....	F	69	..	+	+	.....	Dulness	Coma	.....	Pituitary	Giant-cell granuloma
14	Sheehan and Summers,[3] 1949.....	F	62	..	+	+	.....	Alabaster skin	Coma	.....	Pituitary	Giant-cell granuloma
15	Oelbaum and Wainwright,[2] 1950...	M	29	+	+	+	−30%	.....	Pneumonia; hypopituitarism	Notched incisors; interstitial keratitis	Pituitary; adrenal gland; testis	Giant-cell granuloma
16	Doniach and Wright (Case 1),[4b] 1951	F	43	+	+	+	.....	Headache; chest pain	Coma	Mediastinal nodes	Pituitary; spleen; ? adrenal glands	Giant-cell granuloma
17	Berman,†: J. A. M. A. 147:246, 1951	F	20	..	..	+	.....	Low 17-ketosteroids; positive reaction to water-salt excretion test	Diagnosed by biopsy	Lungs, later	? pituitary; ? lung; ? spleen; eyes; node	Sarcoid; Addison's disease

* Pituitary involvement not confirmed anatomically.
† Case with possible pituitary involvement, not included in text.

ably represent a reaction to a fracture of the vertex of the skull with a possible contrecoup injury of the pituitary gland.[5] It is possible that there is yet another etiological basis for cases of cryptogenic giant-cell granuloma of the pituitary. Sheehan and Summers suggest that, although some of their collected cases may be due to tuberculosis, sarcoidosis or syphilis, others appear to be of a specific disease process of the pituitary gland, the causation of which is unknown. They report two cases of this type.[3] However, in the two similar cases which Doniach and Wright published as of giant-cell granulomata of the pituitary, a granulomatous lesion of the liver was present in one and a similar lesion of the spleen in the other.[4b] The last two cases, therefore, may represent atypical or incompletely studied examples of a systemic disease process, rather than a specific entity affecting only the pituitary gland.

One of the features contributing to the obscurity of this entity is the paucity of reported cases. Haushalter and Lucien, in 1908, reported a case of giant-cell granuloma of the pituitary associated with diabetes insipidus.[6] This syndrome in association with sarcoidosis has become fairly widely recognized.[7] Gougerot and Gy, in 1911, reported an example of cryptogenic granuloma of the pituitary associated with undiagnosed hypopituitarism, but there have been very few reported cases since that time[8] (Table 1). Simmonds, in 1917, reported five asymptomatic cases of giant-cell involvement of the pituitary, collected from 2,000 autopsies.[9] Sheehan and Summers, in 1949, collected 17 cases of active giant-cell granulomata of the anterior pituitary, of which only 6 cases showed neither gumma formation nor caseation. They also listed nine cases of healed granulomata, in six of which, including their own two, the causation was obscure. They cited, in addition, 10 cases of granulomata of the hypothalamus and pituitary which included 2 cases with neither tuberculous nor syphilitic characteristics.[3] When all the possible causes are lumped together, granulomatous involvement of the pituitary is still a very rare entity. We have been able to collect 50 cases from the literature (Tables 1, 2, and 3). The condition in 5 was considered by the authors to be of specific but unknown origin; that in 24 was diagnosed as sarcoid; that in 5 was called tuberculosis, and in 16 cases no specific diagnosis was made.

The purpose of the present communication is to report four cases of cryptogenic giant-cell granuloma of the pituitary, two of which were associated with pituitary deficiency syndromes. Three of these cases were associated with sarcoid-like systemic lesions. It is also desired to emphasize the relative frequency of this lesion in cases of disseminated granulomatous disease which are obviously or possibly sarcoid. Certain observations on the possible etiological basis and clinical significance of this condition will be made.

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5. Berblinger, W.: Zur Hypophysenpathologie: Kompensatorische Hypertrophie von Vorderlappenzellen, Verhandl. deutsch. path. Gesellsch. **22**:191-196, 1927.

6. Haushalter, P., and Lucien, M.: Polyurie simple et tubercle de l'hypophyse, Rev. neurol. **12**:1-6, 1908.

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8. Gougerot, H., and Gy, A.: Insuffisance pluriglandulaire interne thyro-testiculo-surrénale, Nouv. iconog. salpêtrière **24**:449-462, 1911.

9. Simmonds, M.: Ueber das Vorkommen von Riesenzellen in der Hypophyse, Arch. path. Anat. **223**:281-290, 1917.

TABLE 2.—*Reported Cases of Giant-Cell Granulomata of the Pituitary with Diabetes Insipidus*

Case No.	Author; Year	Age	Sex	Maximum Urine Volume, L.	Urinary Specific Gravity	Response to Posterior Pituitary	Clinical Comment	Tuberculous Lesions	Distribution of Granulomata	How Diagnosed	Author's Diagnosis
1	Haushalter and Lucien,[6] 1908.....	47	F	3-4	1.000	.....	Convulsions; coma	Caseous hilar nodes; fibrosis of lungs	Pituitary	Autopsy	Tuberculosis
2	Heerfordt (Case 3),[17d] 1909.....	..	..	5	....	.....	Polyneuritis; well 9 yr. later	.....	? Pituitary; parotid; eyes	Clinically	Uveoparotid fever
3	von Hann,[13b] 1913.....	21	F	8-10	1.000-1.002	Improved	Headaches; spontaneous improvement	Lungs; pleura	Meninges; pituitary	Autopsy	.....
4	von Gierke (Case 1): Verhandl. deutsch. path. Gesellsch. 17:200, 1914	23	F	4-5	1.002-1.004	.....	Headache; visual loss; thyrotoxicosis	? Lung apex	Pituitary	Autopsy	?
5	Gjessing*: Klin. Monatbl. Augenhk. 56:252, 1916	27	F	5	....	.....	Asthenia; fever; cranial nerve pareses	.....	? Pituitary; parotid; eyes	Clinically	Mikulicz syndrome
6	Merrill and Oake*: Am. J. Ophth. 14:15, 1931	..	..	High	....	.....	.....	.....	? Pituitary; parotid; submaxillary nodes; eyes	Clinically	Sarcoid
7	Tillgren (Walgren): Brit. J. Dermat. 47:223, 1935	42	M	6	....	.....	Heart failure	Mesentery; spleen; lungs	Pituitary; skin; lungs; nodes; bones	Autopsy	Sarcoid
8	Lesné, Launay, and Sée,[17e]† 1935....	6	F	3.5	1.001	Improved	Better in 9 mo.	0	? Pituitary; skin; bones	Biopsy of skin	Sarcoid
9	Levin†: J. Nerv. & Ment. Dis. 81:176, 1935	28	F	8-12	....	Improved	Hearing and sensory loss	.....	? Pituitary; parotid; eyes nodes	Clinically	Uveoparotid fever
10	Flandin, Parat, and Poumeau-Delille†: Bull. et. mém. Soc. méd. hôp. Paris 52:1423, 1936.....	56	F	15	1.001	Improved	.....	0	? Pituitary; skin	Biopsy of skin	Sarcoid
11	Falta and Spitzenberger: Strahlentherapie 60:385, 1937.....	43	F	7	1.002-1.005	Improved	.....	? Lung apex; hilar nodes	Pituitary	Autopsy	Sarcoid
12	Waldenström*: Acta med. scandinav. 91:53, 1937	..	..	High	....	.....	High spinal fluid protein	.....	.....	.....	Sarcoid

13	Snapper and Popen*: Pseudo-Tuberculosis in Man, Haarlem, Netherlands, de Erven F. Bohn, 1938, p. 71	16	F	6-8	1.004; conc. to 1.020	.....	"Unquenchable thirst"; amenorrhea 9 mo.; "normal" after 3 yr.	.....	? Pituitary; eyes; ? hilar nodes; skin	Biopsy of skin	Sarcoid
14	Haas †, 1938, cited by Leitner [7]....	..	..	..	....	.....	Infantilism	.....	? Pituitary; ? hypothalamus; eyes; parotid; lacrimal gland	Clinically	.....
15	Arbuse and Madonick†: Am. J. M. Sc. **196**:222, 1938	22	F	6	Conc. to 1.006	Improved	Asthenia	.....	? Pituitary; parotid; eyes; nodes	Clinically	Sarcoid
16	de Morsier and Franceschetti,[17f]† 1938	15	M	6-12	1.003	.....	B. M. R. —11%; small testes; improved in 3 yr.	.....	? Pituitary; parotid; eyes	Clinically	Uveoparotid fever
17	Walsh (Case 6)*: Arch. Ophth. **21**:421, 1939	34	F	Increased	....	.....	Blindness	.....	? Pituitary; skin; eye	Biopsy of eye	Sarcoid
18	Jersild†: Ann. dermat. et syph. **66**:641, 1939	15	M	3-6	1.005	Improved	.....	.....	? Pituitary; parotid; eyes; lungs; nodes; skin	Biopsy of skin	Sarcoid
19	Appelmans and Horenbeeck: Ophthalmologica **102**:65, 1941.....	16	F	High	....	.....	Headache; facial palsy	.....	? Pituitary; parotid; eyes;	Biopsy of conjunctiva	Sarcoid
20	Longcope,[16] 1941	..	..	High	....	.....	.....	.....	Pituitary; hypothalamus ?	Autopsy	Sarcoid
21	Ernsting and Sillevis-Smith†, 1944, cited by Leitner [7].....	31	F	4	Conc. to 1.007	Improved	Cochlear nerve disturbance	.....	? Pituitary; eyes; bones; ? lungs	Clinically	Sarcoid
22	Leitner†: Schweiz. med. Wchnschr. **75**:511, 1945	24	M	4	Conc. to 1.010	.....	Cured of diabetes insipidus in 4 mo.	Lung (later); ? pleura	? Pituitary; eyes; ? lung; skin; ? spleen; parotid	Biopsy of skin and nodes	Sarcoid
23	Rey, Canepa, and Vivoli: Medicina **7**:451, 1947	20	M	3-4	"Low"	.....	.....	Lung (later)	Pituitary; skin; nodes; bones	Biopsy and autopsy	Sarcoid

* Pituitary involvement not confirmed anatomically; diabetes insipidus not well substantiated.
† Pituitary involvemnt not confirmed anatomically.

TABLE 3.—*Reported Symptomless Cases of Giant-Cell Granulomata of the Pituitary Gland*

Case No	Author; Year	Age	Sex	Cause of Death	Tuberculous Lesions	Distribution of Granulomata	Author's Diagnosis
1	Wagner: Arch. Heilk. 3:381, 1862.....	18	F	Convulsion; stupor	Scrofula	Pituitary ?	Tuberculosis
2	Beadles: Brit. M. J. 2:1775, 1896.....	..	..	.....	.....	Pituitary ?	Tuberculosis
3	Lucien and Parisot: Rev. neurol. 17:970, 1909	65	F	Diabetes mellitus	Lungs	Pituitary ?	Tuberculosis
4	Simmonds,[9] 1917	63	F	Strangulated hernia	.....	Pituitary ?	Giant-cell lesion
5	Simmonds,[9] 1917	73	F	Encephalomalacia; arteriosclerosis	.....	Pituitary ?	Giant-cell lesion
6	Simmonds,[9] 1917	61	F	Encephalomalacia; heart disease	.....	Pituitary ?	Giant-cell lesion
7	Simmonds,[9] 1917	50	F	Pyelonephritis; myelitis	.....	Pituitary ?	Giant-cell lesion
8	Simmonds,[9] 1917	49	F	Adrenal hemorrhages; purpura	.....	Pituitary ?	Giant-cell lesion
9	Ricker and Clarke: Am. J. Clin. Path. 19:725, 1949.....	25	..	Sarcoid of the heart	.....	Pituitary; liver; heart; kidneys; lungs; nodes; spleen; brain; pancreas; eyes	Sarcoid
10	Doniach and Wright (Case 2),[4b] 1951.	60	M	Myocardial infarction	.....	Pituitary; ? liver	Giant-cell granuloma
11	Tellum: Acta path. et microbiol. scandinav. 28:294, 1951.....	49	F	Cor pulmonale	.....	Pituitary; liver; lungs; nodes; spleen; adrenal capsule; bone marrow	Sarcoid

REPORT OF CASES

Cases were selected from our files if a granulomatous lesion in the pituitary gland, with associated giant cells and fibrosis, was exhibited. Cases were excluded if there was evident caseous necrosis or if demonstrable acid-fast bacilli in the pituitary, acute miliary tuberculosis, or tuberculous meningitis was found. These cases were arbitrarily excluded from consideration in this series because of the probability that the lesion in the pituitary or its capsule was a manifestation of the generalized meningeal or hematogenous dissemination of tuberculosis, which in an acute miliary stage is often noncaseating and negative to stains for acid-fast bacilli. Cases with the morphologic picture of syphilis—gummatous necrosis, endarteritis, and plasma-cell infiltrate—were also excluded. No cases were included in which there was a fungous infection, foreign-body reaction, or other evident specific cause for a giant-cell reaction.

Fourteen thousand autopsy records from the files of the Mallory Institute of Pathology of the Boston City Hospital, covering the years 1935 to 1950, were screened for examples of granulomatous involvement of the viscera or pituitary. In 12 cases systemic sarcoid-like lesions and pituitaries were available for study. Four of these presented lesions in the pituitary. One additional case of granulomata limited to the pituitary was found. In each of these cases 4 to 10 step sections of the pituitary gland were cut and stained with hematoxylin and eosin, phloxine-methylene-blue, Foote's modification of Hortega's silver carbonate stain for reticulum, and a stain for acid-fast bacilli. In one case there was a granulomatous lesion with caseation but no demonstrable acid-fast bacilli (Table 4). Thus, with exclusion of the last case, almost 30% of our cases with sarcoid-like visceral lesions demonstrated involvement of the pituitary gland.

In one of the cases of disseminated sarcoid-like disease (Case 1) there were symptoms of pituitary insufficiency. In the case of isolated pituitary granulomata (Case 2) features of pituitary insufficiency were likewise demonstrated. Both of these cases are presented in some detail.

CASE 1 (AH-49-11).[10]—*Course.*—I. I., a white housewife 31 years old, was hospitalized in March, 1947, for the treatment of epistaxis, persistent since the removal of obstructing nasal polyps 10 days before. At this time she gave a history of "anemia" and of polydipsia (30 to 40 glasses of water daily) for many years. Catamenia had ceased in April, 1942, when the patient was 26, and she had noted a few hot flashes subsequently, but her libido remained apparently normal. She also recalled on admission an episode of fatigability, drowsiness, constant belching, and hiccoughing in June, 1942, not associated with pregnancy and followed by persistent weakness, waxy pallor, decrease of body weight from 168 to 138 lb. (76.2 to 62.6 kg.), and gradual loss of axillary and pubic hair. She stated that her basal metabolic rate as determined during 1942 "was normal." In 1944 she suffered a transient episode of fever and swelling of cervical nodes. The asthenia had been progressive from that time to the time of admission, and the

TABLE 4.—*New Cases of Giant-Cell Granulomata of the Pituitary Gland*

Case No.	Sex	Age	Symptoms of Pituitary Disease	Symptoms of Systemic Granulomata	Cause of Death	Distribution of Granulomata	Tuberculous Lesions
1	F	33	Weakness; amenorrhea; B.M.R., —22%; polydipsia	None	Panhypopituitarism	Pituitary; lungs; lymph nodes	None
2	M	61	Weakness; pallor; ? loss of hair	None	Hypopituitarism; bronchopneumonia; coronary arteriosclerosis; anemia	Pituitary	None
3	F	72	None	Contributed to cardiac failure	Hypertensive, arteriosclerotic heart disease	Pituitary; heart; spleen	None
4	F	77	None	None	Cerebral hemorrhage	Pituitary; lungs; heart	None
5*	F	64	None	None	? Pernicious anemia; bronchopneumonia	Pituitary; lungs; spleen; liver	? Pituitary

* Not included in the text.

patient complained of palpitation and night sweats. She had had one pregnancy with an uncomplicated delivery in 1934, when she was 18 years old. There was no known family or contact history of tuberculosis.

At first examination (1947) she was alert and well nourished, with well-developed breasts, feminine voice, and no facial hirsutism. Her skin was waxy pale, warm, moist, and smooth, and there was a marked reduction in axillary and pubic hair. There was a solitary, palpable, small axillary node. Her temperature at this time was 99.4 F., her pulse rate, 70, and her blood pressure, 100/70 mm. Hg. There was a little dried blood in the nose and pharynx.

In March, 1947, the urine showed the following: Specific gravity was 1.012; there was no reaction for albumin or sugar, and 3 to 8 white blood cells per high-power field were seen in voided specimens. The hemogram included 10 gm. of hemoglobin per 100 cc., a hematocrit reading of 32%, and a red blood cell count of 3,500,000 per cubic millimeter, with slight anisocytosis and poikilocytosis of the red blood cells. The white blood cell count was 4,380 cells per cubic millimeter, with a differential count of 71% polymorphonuclear leucocytes, 20% lymphocytes, 6% monocytes, and 3% eosinophiles. There were 167,000 thrombocytes (platelets) per cubic millimeter of blood. The clotting time was 2 minutes and the bleeding time 2.5 minutes. The sedimentation rate was 1.45 mm. per minute (Rourke-Ernstein). The serum cholesterol was 139 mg. per 100 cc. The basal metabolic rate was read at —30 and —22%. A 17-ketosteroid

10. This case is presented through the courtesy of Dr. S. Horlick and the Allerton Hospital, Brookline, Mass.

analysis revealed a total of 2 mg. in a 24-hour urine specimen (normal, 5 to 12 mg. in adult women). The fasting blood sugar level was 88 mg. per 100 cc. of serum. The curve for an oral dextrose-tolerance test was flat and prolonged, showing the following levels: One hour, 104 mg.; two hours, 108 mg., and three hours, 87 mg. The skull roentgenograms revealed no changes in the calvarium or tuberculum sellae.

The patient's epistaxis ceased on conservative therapy. It was noted that she did not drink excessively in the hospital. She was referred to the outpatient department with a diagnosis of panhypopituitarism of undetermined cause, but failed to continue her treatment.

She was next seen in July, 1949, because of sore mouth, sore throat, and fever of two weeks' duration, associated with nausea, vomiting, and diarrhea. The interval history revealed an increase of weakness in the two years since her first hospitalization. Examination at this time revealed an extremely ill but moderately well-nourished woman with a waxy pallor, transient cyanosis, and labored breathing. Ulcerated gingivitis was present, in which fusiform bacilli and spirochetes were identified. A few pea-sized submaxillary nodes were palpated. The breasts were well developed. The uterus was small and freely mobile. There was very little axillary and genital hair. The blood pressure was 110/65 mm. Hg. The temperature ranged from 104.2 to 101.8 F. Her pulse rate was 110 to 120, and the respiratory rate was 25 to 32 per minute. The urine was straw-colored and cloudy, with a pH of 4.5, specific gravity of 1.009, and 15 to 20 white blood cells and 1 to 3 red blood cells per high-power field in a voided specimen, but with no reaction for albumin, sugar, or acetone. The hemoglobin level was 13.5 gm. per 100 cc. of blood. The red blood cell count was 3,950,000, and the white blood cell count was 13,400 per cubic millimeter, with 60% polymorphonuclear leucocytes, 10% band forms, 24% lymphocytes, and 4% monocytes. The red blood cells and thrombocytes were apparently normal on smear. The clinical diagnoses were Vincent's angina and panhypopituitarism. The patient was given penicillin, sodium perborate mouth washes, and dextrose solution intravenously, but she remained uncomfortable and complained of extreme weakness. The morning after admission the patient stated that she felt very tired. Late that morning she appeared exhausted. She suddenly became somewhat cyanotic, stated that she was afraid she was going to die, took one gasp, and died.

Autopsy Observations.—Gross Examinations: The necropsy was performed 10 hours after death. Only the pertinent observations will be presented. The body was well developed and well nourished. The skin was very white. There was no axillary and very little pubic hair. The body contours and breasts appeared normal. No lymph nodes were palpable.

The left lung weighed 1,200 gm. and the right 1,500 gm. There were dense apical pleural adhesions. The lungs were dense and subcrepitant and filled in all lobes with bloody fluid, but showed no gross consolidation.

The omentum was adherent to the pelvic organs. There were a few fibrous perisplenic adhesions. The spleen weighed 330 gm. The liver weighed 1,800 gm.

The adrenal glands appeared moderately reduced in weight and size. The cortices averaged 0.1 cm. in thickness and were yellow-gray.

The uterus was small, measuring 8 by 5 by 4.5 cm. The ovaries were also small, measuring 2.2 by 1.5 by 1.2 cm. on the right and 2.0 by 1.2 by 1.0 cm. on the left. They were firm and knobby, without cysts or recent corpora lutea.

The thyroid appeared moderately reduced in size and weight. The gland was pale brown-red and firm.

The pituitary gland was small, but it filled the sella. There was poor demarcation of the anterior from the posterior lobe.

The lymph nodes of the cervical, tracheobronchial, periaortic, iliac, hepatic, and mesenteric regions were increased in number and in size, measuring up to 5 cm. in diameter in the mediastinum. They were discrete, hard or tough, and yellow to gray-white, but not calcified, hemorrhagic, necrotic, or cystic.

Microscopic Examination: The pleurae of the apices were replaced by bands of loose, vascular fibrous tissue, contiguous with fibrosed pulmonary parenchyma. Within the adjacent lung there was a moderately abundant granulomatous inflammation. The granulomata were formed of small, solid clusters of epithelioid cells. Scattered in the granulomata, in fibrous tissue, and in nearby slightly thickened alveolar walls, there were large giant cells of foreign body and Langhans' type, some of which contained small, irregularly lobular, concentrically laminated hyaline bodies. There was an associated diffuse or slightly agglomerated lymphocytic

and monocytic infiltrate. Arteriolar walls in the scarred areas were inconstantly thickened. No asteroid bodies, necrosis, granulocytic infiltrate, calcification, or acid-fast bacilli were identified. The basilar portions of the lungs showed edema and congestion of alveolar capillaries.

No fibrosis or granulomata were present in the spleen. Many of the hepatic portal areas contained somewhat increased amounts of collagen with a few interspersed lymphocytes and plasma cells, but no granulomata were evident.

The renal cortex manifested generalized, apparently edematous thickening of the interstitial tissue without focal scarring or leucocytic infiltrate. Many of the distal convoluted, Henle, and collecting tubules contained a rather large amount of golden-brown, intraepithelial pigment (lipofuscin), but no pigment casts or tubular degeneration or regeneration was apparent.

The adrenal cortex was very thin, and there was no zone of fat-vacuolated cells. A ragged, lipid-poor zona glomerulosa could be made out in a very few areas, and in these areas there was a narrow fascicular zone containing very little lipid. The zona reticularis was relatively thick and ragged, in some areas appearing to replace the zona fasciculata. The adrenal cortex showed general sinusoidal dilatation and increase of loose fibrous tissue. The medulla appeared normal. No leucocytic infiltrate or giant cells were apparent.

The ovarian cortex was thin. There was collagenous fibrosis of the external one-half to two-thirds of the cortex, but the inner portion contained a moderate number of spindly cortical cells and apparently normal ova with tiny collections of granulosa cells. There were a few dense corpora albicantia, but no corpus luteum or evidence of follicle formation was seen.

The thyroid acini were of moderate size and variation in size, and most contained dense basophilic colloid with a few peripheral vacuoles. A few acini contained pink, moderately scalloped colloid. The thyroid epithelium was generally cuboidal. There were prominent collagenous, fibrous interlobular septa.

The vertebral bone marrow was moderately cellular, and maturation appeared regular. There was a slightly increased number of eosinophiles. Lymphocytes were not increased in number, and no granulomata were seen.

The parenchyma of the enlarged lymph nodes of both the chest and the abdomen was largely replaced by a densely fibrosing, granulomatous reaction like that in the lungs. In many of the nodes the capsule and a great number of the sinusoids were intact, but most of the substance was composed of confluent sheets of dense, thick, partially hyalinized collagen fibers interspersed with discrete or confluent nodules of epithelioid cells, some showing transition to dense collagenous tissue. There were a few histiocytes in the centers of some granulomata, and a few contained giant cells. But many other giant cells of foreign-body type and of Langhans' type were scattered in the fibrous tissue of the node. Many of the giant cells contained irregularly nodular, partially laminated, eosinophilic hyaline bodies which filled up to one-half of the cell. No asteroid bodies were identified. There was one small, compact mass of eosinophilic, fibrillar necrosis in the center of one granuloma. No caseous necrosis was evident, and no acid-fast bacilli were evident with appropriate stains.

The outline of the pituitary gland was in general preserved, but the division into lobes and the internal structure were destroyed by a granulomatous, fibrosing inflammatory process (Fig. 1). A few cellular granulomata persisted, but most of the lesions consisted of small nodules of dense, almost acellular collagen which contained very few reticulum fibers. Many foreign-body-type giant cells with laminated inclusions were scattered in areas of moderately dense collagenous fibrosis (Fig. 2). There was a moderate amount of diffuse lymphocytic infiltration. One granuloma contained a tiny area of eosinophilic, fibrillar necrosis within which reticulum fibers were preserved.

Approximately 85% of the anterior lobe and 50% of the posterior lobe of the pituitary gland were replaced by the fibrotic inflammatory process. There were scattered, intact acini of alpha, beta, and chromophobe pituitary cells in the anterior lobe, and there were expanses of normal neural tissue and pituicytes in the posterior lobe, chiefly in the region of the intermediate lobe. There was a large cyst lined by slightly piled-up, ciliated columnar epithelium in the region of the stalk and intermediate lobe, and a number of smaller cysts were present. The capsule of the pituitary contained several paravascular nodules of epithelioid cells, as well as a rather diffuse lymphocytic infiltrate.

There were slight, focal basophilia and loss of striation in muscle fibers of the diaphragm.

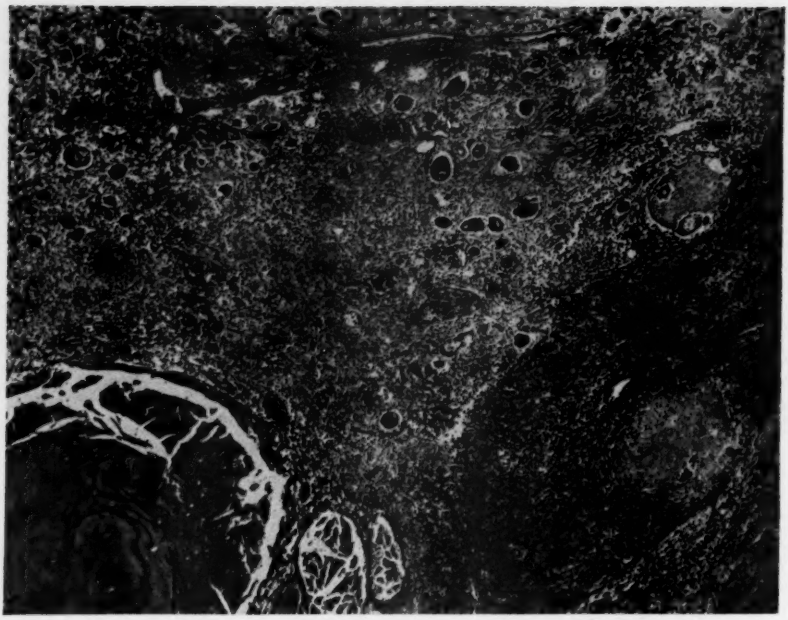

Fig. 1 (Case 1 [AH49-11]).—Pituitary gland, showing fibrosed granulomata, giant cells, fibrosis, and inflammatory infiltrate with destruction of much of the adenohypophysis and neurohypophysis. Phloxine-methylene-blue stain; × 50.

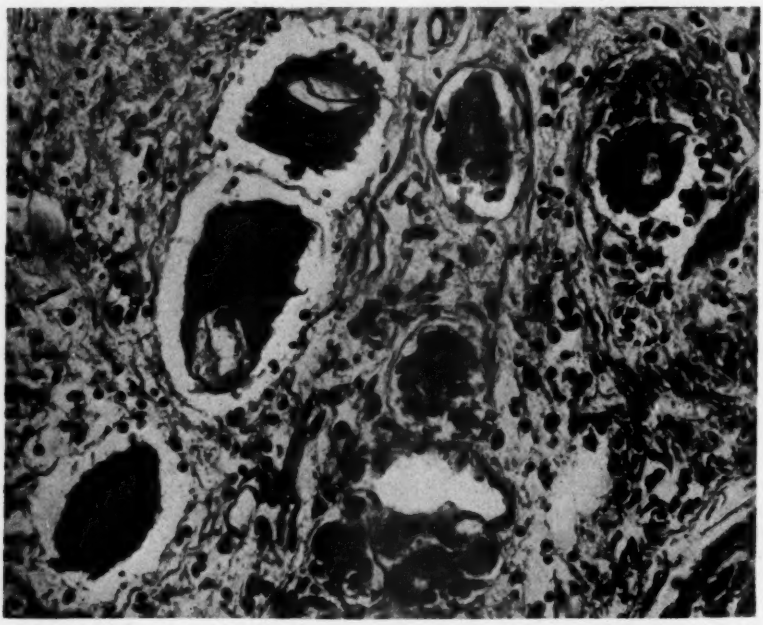

Fig. 2 (Case 1 [AH49-11]).—Pituitary gland, illustrating giant cells with Schaumann inclusions and sparse glandular components in fibrosed stroma. Phloxine-methylene-blue stain; × 400.

The heart, spleen, pancreas, including insular tissue, stomach, meninges, cerebrum, basal ganglia, pons, and skin were not remarkable.

No guinea-pig inoculations of tissue were made.

Anatomic Diagnosis.—The anatomic diagnoses were sarcoidosis involving the pituitary gland, both lungs, and the lymph nodes of the neck, chest, and abdomen; secondary atrophy of the thyroid, adrenal glands, ovaries, and uterus, and Vincent's angina.

CASE 2 (A-37-472).—*Course.*—P. L., an Italian-born white man, was admitted to the Boston City Hospital in 1936 at the age of 59 years, with the chief complaint of weakness of the legs for two years. He had had "poor blood" for several years, and for two years had been taking fresh liver and an iron preparation on the advice of members of the hospital outpatient department. But the weakness, as well as aching in the legs, trembling, and unsteadiness, had persisted, and he was referred to the hospital. The patient recalled "pleurisy" a few years before admission and "flu" in 1918.

Examination on admission revealed a well-developed, well-nourished, elderly white man lying comfortably in bed. Although almost deaf, he seemed alert. The skin was pale but smooth, warm, moderately moist, and without eruptions. The hair of the scalp and body was very sparse, gray, and of fine texture. There was wide flaring of the lower ribs, moderate dorsal kyphosis, and slight increase of anteroposterior diameter of the chest. The breasts were normal for the male. The genitalia were senescent. There was no palpable cervical, axillary, or inguinal lymph node enlargement. The blood pressure was 122/70 mm. Hg. The temperature ranged from 97.4 to 98.7 F. The pulse rate was 62 to 100 per minute, and the respiratory rate was not remarkable.

Laboratory examination showed urines of specific gravity varying from 1.006 to 1.020, and containing no albumin, sugar, cells, or casts. The hemoglobin concentration varied from 10.3 to 12.9 gm. per 100 cc. of blood. The red blood cell count was 4,000,000 per cubic millimeter. The white blood cells totaled 12,000 per cubic millimeter. On numerous differential counts the neutrophiles varied from 21 to 37%, the lymphocytes from 22 to 32%, the monocytes from 2 to 7%, the basophiles from 0 to 3%, and the eosinophiles from 30 to 52%. The extreme eosinophilia was persistent, with no significant change in two weeks. The red blood cells appeared normal, and the thrombocytes were abundant on smear. Barium study of the upper bowel, sigmoidoscopic examination, and stool examinations for blood and parasites were all nonrevealing. The Kahn test gave a negative reaction. No serum agglutinins for typhoid, paratyphoid, or Brucella organisms were found. A serum precipitin test for trichinosis gave a very slightly positive reaction, but the reaction to a skin test was questionable, and a biopsy specimen of the gastrocnemius muscle contained no visible parasites. The patient was discharged, his condition unchanged, with the clinical diagnoses of eosinophilic response to liver therapy and chronic anemia of unknown cause.

He was next admitted to the Boston City Hospital two years later, at the age of 61, because of progression of the pallor and weakness of all four extremities, not improved by liver and iron therapy. Six months before entry, the patient had become mentally depressed, hallucinated, and deluded. On examination at this admission the patient was fairly well nourished but raving and uncooperative. The skin was pale. The hair of body and scalp was sparse. There was hyperemia of the gums, and the margins of the tongue were slightly smooth. The left lung apex was slightly hyperresonant. The blood pressure was 130/85 mm. Hg. The pulse rate was 76 per minute; the temperature was 96 F., and the respirations were 20 per minute. The red blood cell count was 3,800,000 per cubic millimeter, and the hemoglobin level had fallen to 7.2 gm. per 100 cc. of blood. The white blood cell count now was 7,000 per cubic millimeter, with 70% neutrophiles, 28% lymphocytes, and only 2% eosinophiles. The appearance on chest roentgenograms was interpreted as being within normal limits.

Soon after admission the patient became comatose, and he died late on his first hospital day.

Autopsy Observations.—Gross Examination: Postmortem examination was performed 13 hours after death. The patient appeared well developed and fairly well nourished, with a body length of 151 cm. and a weight of 123 lb. (55.8 kg.). There was no palpable lymphadenopathy. A few fibrous adhesions joined both apices of the lungs to the chest wall. The heart weighed 230 gm. The myocardium was dark brown. There was moderate sclerotic thickening of the mitral and aortic valves and of the coronary arteries, with almost complete occlusion of the left descending branch. The right lung weighed 700 gm. and the left 650 gm. Much blood and frothy fluid exuded from the cut surfaces of the dark, subcrepitant lungs. The spleen weighed

70 gm. and the liver 1,000 gm. The adrenal glands were very small and thin, showing apparent atrophy of the cortex. The testes and prostate were of moderate size. The thyroid was not examined. There was very slight fibrous thickening of the pia-arachnoid over the hypothalamus. The pituitary filled the sella and measured 1.5 cm. in greatest diameter. The parenchyma of the anterior lobe of the pituitary appeared to be replaced by a cyst containing viscid material.

Microscopic Examination: Approximately three-fourths of the area of the anterior lobe of the pituitary was occupied by a cyst which was lined by a two-layered epithelium consisting of ciliated columnar cells and small, triangular basement cells. There was a large amount of old, hyalinized scar tissue in the surrounding regions. Under the lining of the cyst and in the nearby tissue, especially toward the pars intermedia, there were scattered hard tubercles consisting

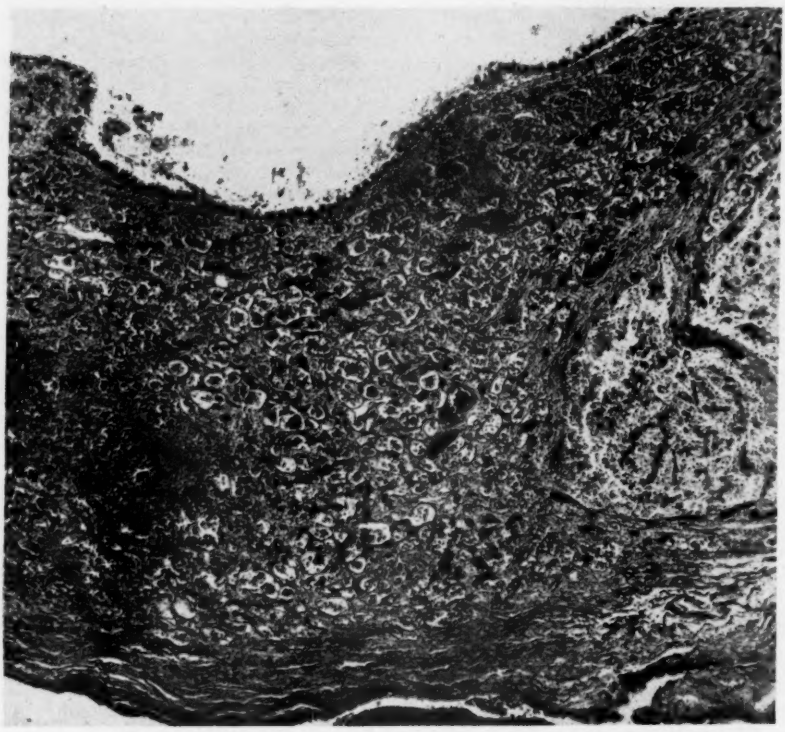

Fig. 3 (Case 2 [A37-472]).—Junction of pars nervosa and pars glandularis, illustrating giant-cell granulomata, one subependymal. Phloxine-methylene-blue stain; × 60.

of plump epithelioid cells, scattered lymphocytes, and occasional giant cells (Fig. 3). A few of the granulomata contained a small amount of central fibrin. No caseation or acid-fast bacilli were found.

The adrenal cortex was decidedly thinned and contained a marked, diffuse lymphocytic infiltration, chiefly in the zone reticularis. There was very little apparent lipid.

Groups of pulmonary alveoli contained masses of polymorphonuclear leucocytes, red blood cells, and fibrin. The vessels of the lungs, spleen, and liver were congested. There was a slightly increased amount of hepatic portal lymphocytic infiltrate, but no granulomata were observed.

The bone marrow was active in both series, but there was a marked increase in both neutrophilic granulocytes and eosinophiles. The marrow contained an increased number of aggregates of lymphocytes. No abnormal erythroid maturation, giant myelocytes, or megaloblasts were seen.

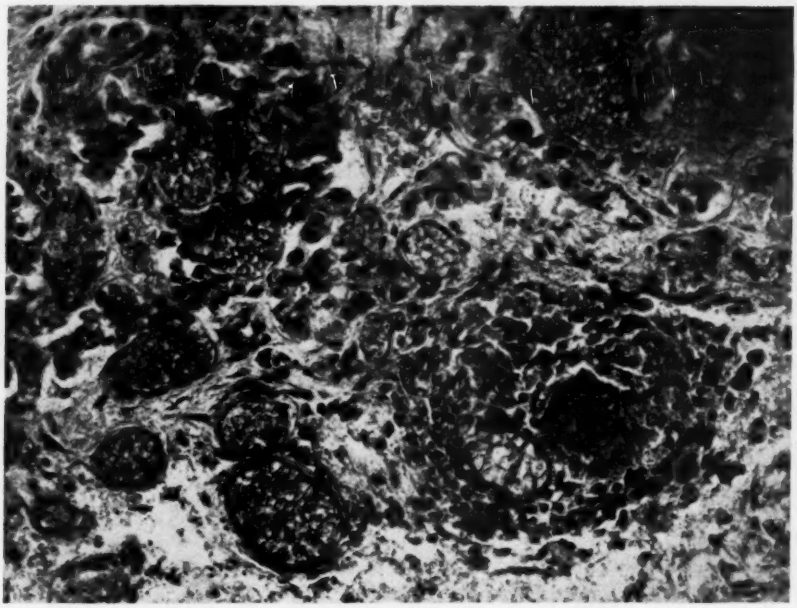

Fig. 4 (Case 3 [A50-321]).—Pituitary gland containing a small paravascular giant-cell granuloma. Phloxine-methylene-blue stain; × 400.

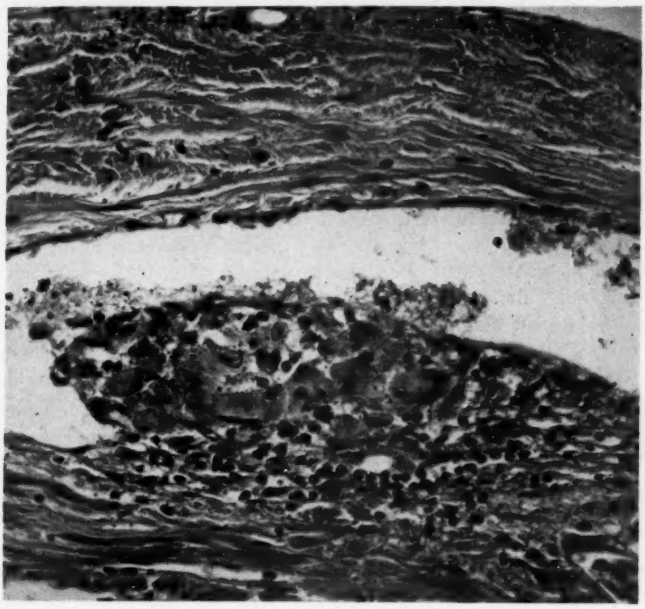

Fig. 5 (Case 4 [A49-705]).—Granuloma of capsule of pituitary. Phloxine-methylene-blue stain; × 400.

The remaining organs were all unremarkable on microscopic examination.

Guinea-pig inoculations were not performed. The heart blood was sterile on routine culture.

Anatomic Diagnoses.—Anatomic diagnoses were giant-cell granulomata of the pituitary gland, secondary atrophy of the adrenal glands, and bronchopneumonia.

In the two additional cases from our files (Cases 3 and 4, Table 4) there was a granulomatous lesion of the pituitary which was apparently symptomless and of no morbid importance (Figs. 4 and 5). In one of these cases there were obscure granulomata in the heart and spleen; in the other the granulomatous disease involved the heart and lungs, in addition to the pituitary. These cases were considered to be of systemic sarcoidosis with involvement of the pituitary gland.

COMMENT

The two detailed cases manifest in common a severe degree of asthenia, striking pallor, loss of body hair, and an otherwise unexplained hypochromic anemia. In each case much of the anterior lobe of the pituitary was destroyed by a fibrosing granulomatous lesion and replaced by a large cystic structure which probably resulted from enlargement of cysts of the pars intermedia. In the first case, involving a 31-year-old woman, amenorrhea, a low basal metabolic rate, and polydipsia were noted. This patient manifested loss of most of the posterior lobe, a lesion which may be correlated with the history of excessive thirst. In the first case there were sarcoid-like lesions in the lungs and lymph nodes. But in the second case only the pituitary gland was demonstrably involved, although there was a history of "pleurisy" in the past. In both cases pituitary insufficiency with associated asthenia and anemia seems to have been a factor contributing largely to the death, associated in the first case with terminal Vincent's angina and in the second with bronchopneumonia.

From the study of our own four cases and those collected from the literature, it appears that nonspecific granulomatous lesions are found in the pituitary gland with relative frequency in the disease complex of sarcoid and occasionally in tuberculosis. Rarely is the process due to syphilis or trauma. Whether, as Sheehan and Summers believe, there is also a specific pituitary giant-cell granulomatous disease cannot be established by the present study. However, the finding of 3 instances of pituitary involvement among 12 cases of a systemic, sarcoid-like disease emphasizes the fact that pituitary granulomata in this systemic disease are not uncommon. This, together with the well-known bizarre patterns of distribution which sarcoid may exhibit, raises the question whether some of the reported instances of isolated pituitary involvement may indeed have been sarcoid.

The cause of the frequency of pituitary localization of these granulomata is not obvious. The causative agent may conceivably be blood-borne, brought by direct contiguity, or transported via the cerebrospinal fluid to the pituitary capsule, itself a derivative of the meninges. A capsular lesion was present in our Case 4, and Schmidtmann reports cases with capsular lesions in tuberculous meningitis[11] (Fig. 5). But the majority of lesions are central. There are reported cases of tuberculosis of the sphenoid bone with direct extension to the pituitary,[12] but no

11. Schmidtmann, M.: Ueber anatomische Veraenderungen des Hirnanhangs bei Tuberkulose, Centralbl. allg. Path. u. path. Anat. **30**:3-7, 1919.

12. Heidkamp, H.: Beitrag zur Tuberkulose der Hypophyse, Arch. path. Anat. **210**:445-461, 1912.

authentic cases of similar extension of a noncaseating lesion have been found. Direct extension of granulomata from the brain to the pituitary may be represented by the reported cases of granulomatous involvement of the hypothalamus and pituitary.[13] It must be assumed that the majority of cases of cryptogenic granuloma of the pituitary have been blood-borne directly to the pituitary, which is rich in vascular sinusoids. The paravascular location of some of the granulomata is corroborative evidence of this theory (Fig. 4). The additional mechanisms of direct extension from the brain and from the pituitary capsule, usually to the posterior lobe, may explain the absence of disproportionate involvement of the sinusoid-rich anterior lobe compared with the posterior lobe.

The severity and relative frequency of clinical symptoms in giant-cell granulomatous disease of the pituitary have scarcely been emphasized in the literature. The collected and reported cases include 18 with symptoms of anterior lobe dysfunction: asthenia, loss of sexual potency, genital atrophy, amenorrhea, loss of sexual hair, or unexplained low basal metabolic rate. In 14 of these cases the hypopituitarism was a major cause of death. In six cases, including our Case 1, death resulted from the peculiar, intractable coma, possibly associated with hypoglycemia, which was first described by Froboese in 1918 in a case of tuberculous destruction of the pituitary gland.[14]

There have been 28 acceptable reported cases of diabetes insipidus with cryptogenic giant-cell disease of the pituitary, including 5 cases (one of them being our Case 1) in which anterior lobe hypofunction was also present.[15] In ten of these cases granulomata were observed in the pituitary at autopsy, and in 18 the granulomatous disease and pituitary involvement were diagnosed clinically by the characteristic picture of systemic sarcoidosis with polyuria and oligosthenuria, often relieved by administration of posterior pituitary (pituitrin®). Biopsy of skin or eye lesions confirmed the diagnosis in eight. It is conceivable that in these last 18 cases hypothalamic involvement may have been a causal factor in the diabetes insipidus, as it probably was in the cases of Longcope,[16] Haushalter and Lucien,[6] and von Hann.[13b]

Coleman and Meredith's patient [1b] with cryptogenic granulomatous involvement of the pituitary had headache and visual loss secondary to the presence of an expanding granulomatous lesion. Surgical treatment effected marked improvement.

Eleven cases of incidental giant-cell granulomata of the pituitary without associated symptoms have been found in the literature, and two more are described. All were diagnosed at autopsy.

There is nothing to set off these cases of cryptogenic granulomatous disease of the pituitary gland from other cases of hypopituitarism, diabetes insipidus, sarcoidosis, or tuberculosis. The sarcoidosis, when present, has been of all degrees of clinical obviousness and importance, oftentimes being entirely asymptomatic and

13. (*a*) Haushalter and Lucien.[6] (*b*) von Hann, F.: Ueber die Bedeutung der Hypophysenveraenderungen bei Diabetes insipidus, Frankfurt Ztschr. Path. **21**:337-365, 1943.

14. Froboese, C.: Die tuberkuloese Erkrankung der Hypophysis, insbesondere ueber die primaere Form, Centrabl. allg. Path. u. path. Anat. **29**:145-152, 1918.

15. (*a*) Kraus.[1a] (*b*) Gougerot and Gy.[8] (*c*) Terpestra, J. J.: Cerebrale stoornissen bij de ziekte van Besnier-Boeck, Nederl. tijdschr. geneesk **88**:476-479, 1944. (*d*) Barber, H. W.: Benign Lymphogranuloma of Schaumann with Apparent Involvement of Anterior Pituitary, Proc. Roy. Soc. Med. **39**:92-93, 1945.

16. Longcope, W. T.: Sarcoidosis, or Besnier-Boeck-Schaumann Disease, J. A. M. A. **117**:1321-1327 (Oct. 18) 1941.

apparently incidental. In general, in those cases with tuberculosis, symptoms of tuberculosis were not numerous or obvious.

There was an important tendency for spontaneous improvement rather than progression in some of these cases.[17] The lesions as seen at necropsy appeared subacute or chronic and as such were associated with some fibrosis. It is possible that during an acute stage, with cellular granulomata and associated diffuse inflammatory response, the clinical picture had been exacerbated, only to improve with subsidence of the inflammatory process. Sarcoidosis has long been known to be a disease of spontaneous regression. This favorable prognostic factor emphasizes the importance of recognition of this granulomatous disease of the pituitary with its associated pituitary dysfunction. It is entirely possible that, through the avoidance of reactions of insulin sensitivity, prompt treatment for the episodes of hypoglycemic coma, and control of intercurrent infections, cases of this type may enter a period of quiescence of the inflammatory process with prolonged survival.

SUMMARY AND CONCLUSIONS

Four new cases of cryptogenic granulomatous involvement of the pituitary gland are reported. Three were associated with a sarcoid-like systemic disease; one appeared confined to the pituitary. In a review of 12 autopsied cases of systemic sarcoid-like lesions, 3 cases of granulomatous involvement of the pituitary and 1 case of bacteria-free, caseous granulomatous involvement have been found.

Fifty cases of giant-cell granuloma, without evident causation, involving the pituitary have been found in the literature. Sixteen of these were associated with hypopituitarism, and 23 had apparently caused diabetes insipidus.[18]

These 54 cases of sarcoid-like granulomatous disease of the pituitary gland probably include some cases of noncaseating tuberculosis of a healed or chronic miliary type, some cases of Besnier-Boeck-Schaumann sarcoidosis, and possibly a case of healed syphilis and one of reaction to trauma. They may also include cases of a primary, specific pituitary parenchymatous degeneration, but such cases become rare with more complete study.

The spontaneous improvement in some of these cases, the development of treacherous hypoglycemia, and the precipitation of fatal coma by infection indicate the importance of prompt recognition of this disease.

Miss Lillian M. Leavitt performed the special histologic procedures. Mr. Leo Goodman made the photographs.

17. (*a*) Gougerot and Gy.[8] (*b*) von Hann.[13b] (*c*) Footnote 15*c* and *d*. (*d*) Heerfordt, C. F.: Ueber eine "Febris uveo-parotidea subchronica," von Graefes Arch. Ophth. **70**:254-273, 1909. (*e*) Lesné E.; Launay, C., and Sée, G.: Diabète insipide au cours d'une maladie de Besnier-Boeck, Bull. et mém. Soc. méd. hôp. Paris **51**:1137-1146, 1935. (*f*) de Morsier, G., and Franceschetti, R.: La neuro-uvéo-parotidite: Maladie de Heerfordt avec syndrome hypothalamique, Rev. neurol. **69**:688-692, 1938.

18. Since submitting this article, we have recognized three additional reported cases of diabetes insipidus with systemic sarcoid granulomata: Pennell, W. H.: Boeck's Sarcoid with Involvement of Central Nervous System, A. M. A. Arch. Neurol. & Psychiat. **66**:728-737 (Dec.) 1951 (clinical evidence of pituitary and lung involvement and histologic evidence of lymph node granulomata); Posner, I.: Sarcoidosis: Case Report, J. Pediat. **20**:486-495, 1942 (autopsy confirmation of granulomata involving viscera, pituitary, and bones), and Sands, I. J., and Riley, H. A.: Boeck's Sarcoid with Neurologic Manifestations, Tr. Am. Neurol. A. **68**:57-63, 1942 (biopsy evidence of eye involvement and clinical indications of pituitary and small bone involvement).

EFFECT OF ACUTE HYPOTENSION ON CEREBRAL HEMODYNAMICS AND METABOLISM OF ELDERLY PATIENTS

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OUR RECENT observations [1] have shown that the cerebral blood flow and metabolism in persons over 50 years of age with evidence of cerebral vascular disease is significantly reduced from that of both normal young and elderly patients. It is conceivable that elderly patients with hypertension and cerebral arteriosclerosis may be unable to compensate by vasodilatation for a relatively sudden decrease in systemic blood pressure. Under such conditions a pathologically more sluggish cerebral circulation may result which may predispose to the formation of cerebral thrombosis. It was thought that studies of the effect of artificially induced hypotension on cerebral hemodynamics in this group of patients might help to elucidate the problem.

METHOD

Subjects selected for this study were over 50 years of age and had hypertension (mean arterial pressure over 110 mm. Hg) and cerebral vascular disease. The latter was determined by the presence of any two of the following criteria: (1) old or recent cerebral vascular accident; (2) eyeground changes consistent with arteriosclerotic retinopathy, Grade II or more; (3) mental changes attributable to senility. The nitrous oxide procedure for the determination of cerebral blood flow as devised by Kety and Schmidt [2] and modified by Scheinberg and Stead [3] was employed. Values for cerebral blood flow (CBF in ml. blood/100 gm. brain./min.), cerebral vascular resistance (CVR in mm. Hg/ml. blood/100 gm. brain/min.), and cerebral metabolic

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The tetraethylammonium chloride (TEAC) used in this study was supplied by Parke, Davis & Company, Detroit 32.

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From the Medical Division of Gallinger Municipal Hospital (Dr. Bessman, Fellow in Medicine, George Washington University; Dr. Alman, formerly Chief Medical Officer, Out Patient Department, and Dr. Fazekas, Chief of Staff, Gallinger Municipal Hospital).

1. Fazekas, J. F.; Alman, R. W., and Bessman, A. N.: Cerebral Physiology of the Aged, Am. J. M. Sc. **223**:245, 1952.

2. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure and Normal Values, J. Clin. Invest. **27**:476, 1948.

3. Scheinberg, P., and Stead, E. A., Jr.: The Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique: Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization and Peripheral Resistance, with Observations on the Effect of Tilting and Anxiety, J. Clin. Invest. **28**:1163, 1949.

rate (CMR-O_2 in ml. O_2/100 gm. brain/min.) were calculated as described by the above authors. Mean arterial pressure (MAP) was read from a damped aneroid manometer attached to a needle in the femoral artery. Blood-gas analyses were made as previously described.[2]

After an initial control study of the cerebral blood flow, metabolism, and vascular resistance, the patients rested for 30 minutes to insure complete pulmonary excretion of the nitrous oxide. At this time an intravenous injection of tetraethylammonium chloride (TEAC) was given until a drop in the mean arterial pressure of more than 30 mm. Hg was obtained. The total duration of hypotension ranged from 20 to 30 minutes. The dose of tetraethylammonium chloride injected was dependent on the patient's response and varied widely. In no instance was more than 5 mg. per kilogram of body weight given.

RESULTS

Only 2 of the 12 patients studied failed to show a significant decrease in blood pressure following administration of the drug. A summary of the data on those patients in whom hypotension developed after administration of tetraethylammonium chloride is presented in Table 1. After injection of the drug, there was a fall in blood pressure from a mean of 133 mm. Hg to a mean of 87 mm. Hg. Thus, a mean decrease of 46 mm. Hg was obtained, with a maximum fall of 75 and a minimum fall of 30 mm. Hg. With the exception of the cerebral vascular resistance, the cerebral hemodynamic functions following this abrupt drop in blood pressure were unchanged. The cerebral blood flow showed no significant ($P > 0.05$) change after administration of tetraethylammonium chloride, the mean value being 33.4 ml. blood/100 gm. brain/min., as compared with the control value of 39.4 ml. blood/100 gm. brain/min. The cerebral metabolic rate likewise demonstrated no significant ($P > 0.05$) change, the control value being 2.3 ml. O_2/100 gm. brain/min., and the experimental value, 2.4 ml. O_2/100 gm. brain/min. Although the cerebral blood flow remained essentially unchanged when the group is taken as a whole, in two patients there was a marked decrease in cerebral blood flow. Patient 9 showed a 50% fall in cerebral blood flow (control value 60.4; experimental value, 30.2 ml. blood/100 gm. brain/min.), while Patient 7 showed a decrease in cerebral blood flow of 36% (control value, 35.3; experimental value, 22.6 ml. blood/100 gm. brain/min.). In both patients the cerebral metabolic rate remained essentially unchanged. Since the marked decrease in cerebral blood flow was inconsistent with the other data, studies on Patient 9 were repeated, and comparable results were obtained (these results are not included in Table 1). The changes in cerebral blood flow and cerebral arteriovenous oxygen differences were inversely proportional but so small as to be insignificant; it is conceivable that in a much larger series these small changes might become significant—the net result still being that the cerebral metabolic rate would remain unchanged.

The only consistent alteration in cerebral hemodynamics occurring as the result of an acute fall in systemic blood pressure was the decrease in cerebral vascular resistance. This decrease from the mean control value of 3.8 mm. Hg/ml. blood/100 gm. brain/min. to a mean experimental value of 2.8 mm. Hg/ml. blood/100 gm. brain/min. was statistically significant ($P < 0.01$), a fall of more than 25%.

In every patient except two, despite the fact that the cerebral oxygen utilization and blood flow remained remarkably constant, signs and symptoms ordinarily ascribed to cerebral anoxia,[4] such as yawning, increased confusion, nausea, vomiting, increased emotional instability, and/or the onset of Cheyne-Stokes respiration,

4. Sodeman, W. A.: Pathologic Physiology: Mechanisms of Disease, Philadelphia, W. B. Saunders Company, 1950.

TABLE 1.—*Effect of Hypotension Induced by Tetraethylammonium Chloride on Cerebral Hemodynamics*

Patient	Age	Diagnosis *	State of Consciousness †	MAP ‡ C	MAP ‡ E	CBF C	CBF E	CVR C	CVR E	CMR C	CMR E	A-VO_2 C	A-VO_2 E	Side-Effects
1	56	CVA; HCVD; general AS	1+	148	101	30.0	26.0	4.9	3.8	2.4	2.2	8.12	8.61	Yawning
2	80	HCVD, general AS	1+	155	114	43.5	39.2	3.5	2.9	2.2	2.2	5.07	5.70	Shaking chill and confusion
3	53	Cerebral and general AS; old CVA	1+	118	67	21.4	17.5	5.5	3.8	1.0	1.7	5.05	9.04	Cheyne-Stokes respirations
4	63	HCVD; AS; mild diabetes	0	135	105	33.6	39.5	4.0	2.6	2.2	2.6	6.73	6.81	None
5	75	HCVD; CVA (recent thrombosis)	1+	124	90	38.6	36.4	3.2	2.4	1.6	2.0	4.34	5.64	Yawning, shaking chill
6	57	HCVD; CVA (hemorrhage)	1+	168	98	50.6	51.3	3.2	1.9	1.9	1.6	3.78	3.18	Became 2+, 1+ as blood pressure increased
7	65	HCVD; CVA (hemorrhage)	2+	139	64	35.3	22.6	3.9	2.8	2.8	2.4	7.83	10.59	Cheyne-Stokes respirations
8	70	HCVD; pellagra	1+	118	86	45.9	43.0	2.5	2.0	3.7	3.5	8.19	8.18	Psychotic, very uncooperative
9	72	AS; CVA (thrombosis)	1+	110	73	60.4	30.2	1.8	2.4	3.2	3.0	5.33	10.04	Cheyne-Stokes respirations
10	64	AS; CVA (thrombosis)	1+	118	70	34.8	29.2	3.4	2.4	2.4	2.7	6.87	9.24	None
Mean	66			133	87§	39.4	33.4	3.8	2.8§	2.3	2.4	6.14	7.78	

* CVA means cerebral vascular accident; HCVD, hypertensive cardiovascular disease; AS, arteriosclerosis.
† 0 indicates alert, oriented; 1+, confused, disoriented; 2+, semicomatose.
‡ C means control; E, experimental. MAP is mean arterial pressure in millimeters of mercury; CBF, cerebral blood flow in ml. blood/100 gm. brain/min.; CVR, cerebral vascular resistance in mm. Hg/ml. blood/100 gm. brain/min.; CMR, cerebral metabolic rate in ml. O_2/100 gm. brain/min., and A-VO_2, arteriovenous oxygen difference in volumes per cent.
§ Significant change ($P < 0.01$).

TABLE 2.—*Effect of Tetraethylammonium Chloride Administration on Cerebral Hemodynamics Without Hypotension* *

Patient	Age	Diagnosis	State of Consciousness	MAP C	MAP E	CBF C	CBF E	CVR C	CVR E	CMR C	CMR E	A-VO_2 C	A-VO_2 E	Side-Effects
1	47	HCVD; 3 CVA's (thrombosis)	0	110	95	38.0	34.0	2.9	2.8	0.8	1.4	2.69	4.12	None
2	59	Hypertension; CVA; aphasia	1+	114	101	42.5	37.6	2.6	2.6	1.7	1.6	4.10	4.36	Shaking chill

* Symbols are explained in footnotes to Table 1.

were noted during the period of decreased blood pressure. One patient (8), who had been very confused, became actively psychotic with paranoid delusions. Another patient (not included in the series) became nauseated and vomited during the period of hypotension, necessitating discontinuance of the procedure. Of the two patients in whom no changes of cerebral function were observed, one (Patient 4) was the only subject of the entire series in whom the state of consciousness in the control phase seemed unimpaired.

A summary of the data obtained from the two patients in whom there was no hypotensive response to the injection of tetraethylammonium chloride is presented in Table 2. There was no significant change in any of the cerebral hemodynamic functions, nor was there any evidence of derangement of cerebral function.

In 4 of the 12 patients receiving tetraethylammonium chloride, i. e., 33.3%, an apparently unusual reaction was observed. The patients first began to complain of feeling chilly about 10 minutes after discontinuance of administration of the drug, often just as the blood pressure was beginning to rise. Approximately five minutes later severe shaking chills ensued, lasting 5 to 20 minutes. The blood pressure invariably had returned to control levels after the chill. The reaction apparently bore no relation to the fall in blood pressure, as it was seen in one subject without the depressor response. No subsequent temperature elevations nor any further untoward reactions were noted.

COMMENT

Relaxation of the increased cerebral vascular tonus in patients with apparently uncomplicated hypertension in response to a sudden drop in blood pressure (of similar magnitude as in our series) has been demonstrated by Hafkenschiel with the use of dihydroergocornine.[5] In his studies the cerebral vascular resistance decreased sufficiently to compensate fully for the induced hypotension, the cerebral blood flow thereby remaining constant. After sympathetic block in young patients with hypertension, the relaxation of the cerebral vessels apparently only partially compensates for the fall in blood pressure, since there is a slight but significant decrease in cerebral blood flow.[6]

It has also been shown that the cerebral vessels of arteriosclerotic patients respond to the inhalation of 5% carbon dioxide with an increase in the cerebral blood flow and a decrease in the cerebral vascular resistance.[1] The mean increase in cerebral blood flow in this group of patients, however, is considerably less than that observed in similar circumstances in younger patients without cerebral vascular disease [7] (35% and 75% mean increase in cerebral blood flow, respectively). Furthermore, there are a few elderly arteriosclerotic patients in whom no measurable vasodilatation is produced by inhalation of 5% carbon dioxide.

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5. Hafkenschiel, J. H.; Crumpton, C. W.; Moyer, J. H., and Jeffers, W. A.: The Effects of Dihydroergocornine on the Cerebral Circulation of Patients with Essential Hypertension, J. Clin. Invest. **29**:408, 1950.

6. Kety, S. S.; King, B. D.; Horvath, S. M.; Jeffers, W. A., and Hafkenschiel, J. H.: The Effects of an Acute Reduction in Blood Pressure by Means of Differential Spinal Sympathetic Block on the Cerebral Circulation of Hypertensive Patients, J. Clin. Invest. **29**:402, 1950.

7. Kety, S. S., and Schmidt, C. F.: The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men, J. Clin. Invest. **27**:484, 1948.

In light of the above, it was anticipated that the abnormal cerebral vessels of the elderly arteriosclerotic patient might not be able, by relaxation, to compensate completely for the decreased blood pressure. However, such was not usually the case, and a constant cerebral blood flow, as well as metabolic rate, was maintained, apparently by virtue of the marked decrease in cerebral vascular resistance. The two cases in which there was noted a significant decrease in cerebral blood flow may bear some relation to the above-mentioned finding that some arteriosclerotic patients do not respond to inhalation of 5% carbon dioxide. It would seem that most arteriosclerotic patients can respond by vasodilatation of their cerebral vessels to stimuli, e. g., sudden hypotension or inhalation of 5% carbon dioxide. However, there seems to be a group of such patients in whom the organic changes of the cerebral vessels are so advanced and widespread that dilatation and relaxation of these vessels are restricted. It may well be that this is the type of patient in whom thromboses develop during sleep because of the failure of compensatory mechanisms.

The mean value of 3.8 mm. Hg/ml. blood/100 gm. brain/min. for cerebral vascular resistance seen in this group of patients is abnormally high as compared with that in younger subjects, but coincides with the value for cerebral vascular resistance in subjects over 50 years of age with evidence of cerebral vascular disease, but normal mental status (mean cerebral vascular resistance, 3.8 mm. Hg/ml. blood/100 gm. brain/min.), and in subjects over 50 years of age with evidence of cerebral vascular disease and mental changes of confusion and disorientation (mean cerebral vascular resistance, 3.6 mm. Hg/ml. blood/100 gm. brain/min.).[1] Whether the decrease of cerebral vascular resistance (representing vasodilatation) which was observed after the administration of tetraethylammonium chloride and the production of hypotension results from partial relaxation of secondary spasm of the involved vessels, or whether it is more likely due to active dilatation of less severely affected (or normal) vessels, cannot be stated with any degree of certainty at this time.

Despite the presence of quantitatively unchanged cerebral hemodynamics, 80% of the patients in our series manifested subjective and objective signs ordinarily attributed to cerebral anoxia during the period of hypotension. This is in marked contrast to the low incidence of such manifestations in other series in which hypotension of similar magnitude was produced in young persons.[8] Further, it should be borne in mind that one of the two patients who failed to show such symptoms was the only patient of the series who was fully alert. All other subjects showed varying degrees of cerebral functional derangement in the resting state (confusion, disorientation, etc.). In a recent publication by Denny-Brown [9] it was pointed out that "the most dramatic worsenings when cerebral hemodynamics are already compromised were related to the falls of blood pressure accompanying syncope . . ., gastrointestinal hemorrhage . . ., and sleep." We feel that the vasodilatation produced in our patients with arteriosclerosis may occur chiefly in the less diseased vessels and at the expense of a further impairment of circulation through the more severely involved vessels. Stagnant anoxia may occur locally but may be unmeasurable by the technique employed. Thus, despite an apparently unchanged total cere-

8. Hafkenschiel and others.[5] Kety and others.[6]

9. Denny-Brown, D.: The Treatment of Recurrent Cerebrovascular Symptoms and the Question of "Vasospasm," M. Clin. North America **35**:1457, 1951.

bral blood flow and cerebral metabolic rate, the blood flow in already compromised areas may be further decreased, and such apparent homeostasis may be misleading in terms of local function.

The data obtained in this study suggest that most arteriosclerotic patients are able to compensate by vasodilatation for an abrupt hypotension of short duration and thus maintain a stable total cerebral blood flow and cerebral metabolic rate. It is conceivable, however, that the compensatory mechanisms utilized would be inadequate in the face of more prolonged episodes of decreased blood pressure (e. g., those occurring during sleep or induced by hypotensive agents), and studies are in progress to investigate this possibility.

CONCLUSIONS

Cerebral blood flow, cerebral metabolic rate, and cerebral vascular resistance were studied in 12 hypertensive patients over 50 years of age with evidence of cerebral arteriosclerosis before and after administration of tetraethylammonium chloride.

Ten of the 12 patients experienced a fall in blood pressure of more than 30 mm. Hg. In these 10 patients, the cerebral vascular resistance decreased significantly, while the cerebral metabolic rate and cerebral blood flow remained statistically unchanged. These studies suggest that the cerebral blood vessels of most elderly arteriosclerotic patients are capable of relaxation in response to a sudden drop in blood pressure, thus preventing a fall in cerebral blood flow which would otherwise occur. The possible significance of the accompanying signs and symptoms of cerebral anoxia is discussed.

PERFORATION OF THE INTERVENTRICULAR SEPTUM

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PERFORATION of the interventricular septum is an uncommon complication of myocardial infarction. Sager [1] reviewed 18 cases in a survey of the literature in 1934. Weber [2] listed 17 more patients in 1943. Additional reports [3] have increased

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1. Sager, R. V.: Coronary Thrombosis: Perforation of the Infarcted Interventricular Septum, Arch. Int. Med. **53**:140-152 (Jan.) 1934.

2. Weber, M. L.: Perforation of the Interventricular Septum Following Infarction: Intravitam Diagnosis; Report of a Case and Survey of the Literature, Ann. Int. Med. **19**:973-989, 1943.

3. (*a*) Leonard, B. W., and Daniels, W. B.: Perforation of the Interventricular Septum Caused by Coronary Occlusion: Report of a Case, Am. Heart J. **16**:751-754, 1938. (*b*) Liesch, E., and Carere-Comes, O.: Rottura del setto interventricolare in soggetto con aterosclerosi coronarica, ipertrofia miocardica e aneurisma parietale del cuore (Considerazioni cliniche ed anatomopatologiche), Riv. clin. med. **39**:283-326, 1938. (*c*) Edmondson, H. A., and Hoxie, H. J.: Hypertension and Cardiac Rupture: A Clinical and Pathologic Study of 72 Cases, in 13 of Which Rupture of the Interventricular Septum Occurred, Am. Heart J. **24**:719-733, 1942. (*d*) Wood, F. C., and Livezey, M. M.: 5-Year Survival After Perforation of Interventricular Septum Caused by Coronary Occlusion: Histologic Study of Kidneys After 350 Injections of Mercurial Diuretics, ibid. **24**:807-815, 1942. (*e*) Schwarts, L. S.: Diagnosis During Life of Perforation of the Interventricular Septum, Sovet. med. (Nos. 10-11) **8**:24-25, 1944. (*f*) Wood, A. M.: Perforation of the Interventricular Septum Due to Cardiac Infarction, Brit. Heart J. **6**:191-193, 1944. (*g*) Master, A. M., and Russell, T. B.: Acute Coronary Artery Occlusion with Intraventricular Septal Perforation, Bernheim Syndrome and Superior Vena Cava Obstruction, Diagnosed Clinically, Ann. Int. Med. **22**:440-447, 1945. (*h*) Lober, P., and Hertzog, A. J.: A Case for Diagnosis, Minnesota Med. **28**:733-735, 1945. (*i*) Lian, C.; Welti, J. J.; Baraige, E., and Rousseau, G.: Apropos d'un cas de perforation septale par infarctus du myocarde (avec présentation de pièce), Arch. mal. cœur **39**:163-167, 1946. (*j*) Moia, B., and Alvarez, A. J.: Comunicación interventricular adquirida por ruptura de infarto de miocardio, Rev. argent. cardiol. **13**:110-117, 1946. (*k*) Foster, L.: Spontaneous Rupture of the Heart: Clinical-Pathological Correlation with Presentation of 12 Cases, Quart. Bull. Northwestern Univ. M. School **20**:209-214, 1946. (*l*) Shapiro, Y. E., and Nemirovsky, Y. A.: Clinical Aspects and Intravital Diagnosis of Perforation of the Interventricular Septum in Myocardial Infarction, Vrach. delo (Nos. 2-3) **27**:165-170, 1947. (*m*) Diaz-Rivera, R. S., and Miller, A. J.: Rupture of the Heart Following Acute Myocardial Infarction: Incidence in a Public Hospital, with Five Illustrative Cases Including One of Perforation of the Interventricular Septum Diagnosed Ante Mortem, Am. Heart J. **35**:126-133, 1948. (*n*) Fowler, N. O.,

(*Footnote continued on next page*)

the number of recorded cases of perforation of the infarcted septum to 75, in 28 of which the diagnosis was made ante mortem.

It is the purpose of this communication to present two additional cases of myocardial infarction with rupture of the interventricular septum. The first is unusual because of a four-and-one-half-year survival. In the other, in which diagnosis was made during life, the perforation was caused by marked atherosclerotic narrowing of an unusual septal branch of the left anterior descending coronary artery.

REPORT OF CASES

CASE 1.[4]—M. R., a 56-year-old white man, was first admitted to the Beth Israel Hospital on Feb. 27, 1931, complaining of increasing dyspnea and cough for eight months. In July, 1930, he had experienced an attack of "acute indigestion" associated with severe precordial pain. This was diagnosed as a coronary thrombosis by his private physician. After that time the patient had noted increasing dyspnea on moderate exertion, with the development of marked pedal edema and orthopnea. He also had occasional precordial pain and palpitation. In addition, he had had a severe persistent cough productive of thick, greenish sputum. His previous medical history was not contributory.

Examination revealed a markedly dyspneic and orthopneic man, with moderate cyanosis of the lips and nail beds. The chest was emphysematous, with numerous crepitant rales and rhonchi throughout both lung fields. A systolic thrill was palpated over the cardiac apex. There was a blowing apical systolic murmur, seeming to extend into diastole. The murmur was transmitted to the axilla. The second pulmonic sound was accentuated. The rhythm was regular. The blood pressure was 130/90. The abdomen showed marked distention; the liver and spleen were not palpable. There was ankle edema (4+), bilaterally. A diagnosis of rheumatic heart disease, mitral stenosis and insufficiency, and marked cardiac decompensation was made. The patient improved with bed rest and injections of mersalyl (salyrgan®). He was discharged on March 16, 1931.

On April 29, 1931, he returned to the hospital, complaining of swelling of the abdomen and legs, associated with precordial pain, cough, dyspnea, and orthopnea. Physical findings were similar to those on the previous admission. A long, loud murmur, both systolic and diastolic, was heard at the apex, and a systolic murmur was audible at the base. No mention was made of a thrill. The blood pressure was 135/108. Marked abdominal distention suggested the pres-

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4. Dr. David Ball supplied data on the first and second hospital admissions in this case. Dr. Albert Plaut, former Pathologist at Beth Israel Hospital, called our attention to this case.

ence of ascites. With digitalization and the administration of mercurial diuretics, the patient had a diuresis and weight loss of 15 lb. (6.8 kg.). He was discharged on May 27, 1931, to the care of his private physician.

The patient's final admission to the hospital was on Dec. 27, 1934. His complaints included abdominal pain for two months and dyspnea, ankle edema, and swelling of the abdomen for three months. For about two years after his last previous hospitalization he had been able to get about slowly, although dyspnea on moderate exertion was always present. During the three months prior to this third admission, symptoms of congestive failure had increased. For these symptoms he had received mersalyl. About two months before admission he began to have pain in the right upper quadrant of the abdomen, which was worse after eating and was associated with occasional nausea and several episodes of vomiting.

Examination revealed a well-developed, elderly, orthopneic, and moderately dyspneic man complaining of constant right upper abdominal pain. The temperature was 102.4 F.; respirations numbered 24 per minute; the pulse rate was 90 per minute, and the blood pressure was 130/80. With the patient in a sitting position, the neck veins were distended. Throughout both lung fields there were numerous sibilant and occasional crepitant rales. The breath sounds were diminished at both bases. The point of maximum impulse of the heart was in the sixth intercostal space at the left anterior axillary line. A systolic thrill was felt in this area. The rhythm was regular. A long systolic murmur was heard at the apex and was transmitted to the axilla. It was followed by a short diastolic murmur. There was a systolic murmur at the base. The second pulmonic sound was present, but the second aortic sound was not audible. Palpation of the abdomen elicited marked generalized rebound tenderness but no rigidity. There was exquisite tenderness in the right upper quadrant, where the liver edge was palpable 3 cm. below the costal margin, and a hard, lemon-sized gall bladder could be felt.

Laboratory data included a normal hemogram; the venous pressure was 16.5 cm. of water, and the arm-to-tongue circulation time (calcium gluconate) was 27 seconds. A roentgenogram of the chest revealed diffuse pulmonary congestion and considerable left ventricular enlargement. The electrocardiogram, consisting of standard limb leads only, showed right bundle branch block with a QRS interval of 0.12 second.

The patient's course was marked by the development of jaundice shortly after admission, associated with low-grade, intermittent fever. He then appeared to be improving, but on the 10th hospital day there was a sudden febrile spike to 104 F. On the 14th hospital day he experienced severe pain in the right upper abdomen. Laparotomy disclosed a distended, thickened, and congested gall bladder, with inspissated bile and many small biliary concretions. A cholecystostomy was performed. After the operation the patient had marked dyspnea with many moist rales throughout both lung fields. Despite supportive measures, he died on the 15th hospital day.

Autopsy Observations.—At autopsy the heart was enlarged, measuring 15 by 13 by 8 cm. The internal surface of the pericardium was smooth except for a small, roughly circular area about 2.5 cm. in diameter where the apex of the heart was bound to the pericardial sac by readily broken pinkish-gray adhesions. The apex, which was formed solely by the left ventricle, appeared as a gray, rounded, sac-like bulge which was fluctuant. The right atrium was wide. The cavity of the right ventricle was markedly dilated. The wall was hypertrophied, reaching a thickness of 0.7 cm. The trabeculae were considerably thickened, some being 1.5 by 1 cm. on cross section. The left atrium was dilated. No abnormalities were noted in the mitral leaflets, apart from some atheromatous deposits. The cavity of the left ventricle was wide and long. In its upper part the wall reached a thickness of 1.7 cm. The apex, however, was a thin-walled, ovoid sac, 8 by 5 by 4 cm., with the muscle completely replaced by fibrous tissue only 2 mm. thick. The posterior wall of this sac was formed chiefly by the lower half of the interventricular septum to within 4 cm. of the base of the aortic valves. The gradation from muscle to fibrous tissue was fairly abrupt, being marked by a 1-cm. zone of thickened endocardium and atrophied trabeculae surrounding the sac on the left ventricular aspect; in the left half of the right ventricle this thickening covered nearly one-third of the endocardium. The inner aspect of the sac was smooth and pinkish-gray, with occasional firm, raised, yellowish areas and several thin, small, false chordae near its upper posterior wall. Two and five-tenths centimeters below the upper edge of the septal portion of the aneurysm, there were two ovoid openings, 1.75 by 1 and

1 by 0.5 cm., respectively, with smooth edges and a narrow fibrous bridge 2 mm. thick between them, thus forming two interventricular defects (Fig. 1). A probe passed through the larger opening from the left ventricle entered directly into the lower part of the right ventricle 2 cm. above its apex. A probe through the smaller defect entered a longer channel separated from the former by thickened trabeculae. Coursing upward to the right of the interventricular septum, it opened into the cavity of the right ventricle 3 cm. below the pulmonic valves. The endocardium of the right ventricle in the region of the larger opening was markedly thickened, and the trabeculae were fibrosed. The myocardium was firm and reddish-brown. Apart from the general hypertrophy and the changes noted above, it showed little abnormality to the naked eye. The papillary muscles were thick and dark brown, with grayish tips. The chordae tendineae were slightly thickened. The coronary arteries were wide at their commencement and had numerous small atheromatous plaques along the course of their larger branches. Six centimeters from its origin the left anterior descending branch was completely occluded. On section it appeared homogeneously yellowish-gray, and the site of its former lumen could not be recognized. The remaining coronary arteries showed no other abnormalities.

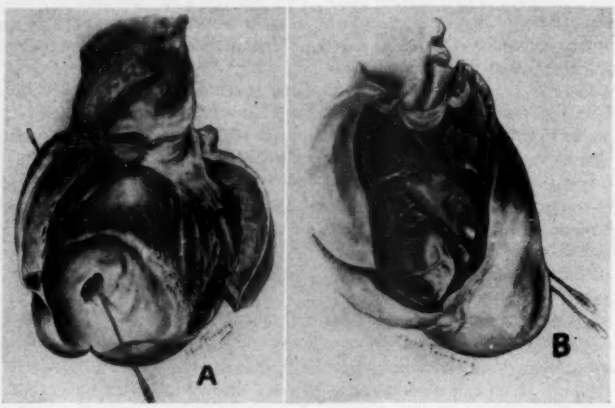

Fig. 1 (Case 1).—*A* shows anteroseptal aneurysm of left ventricle, with two ovoid septal defects separated by narrow fibrous bridge. Probe through larger, lower defect passes into lower portion of right ventricle (*B*), while probe in upper defect traverses a longer channel to emerge 3 cm. below pulmonic valve.

Other findings included severe, partly necrotizing cholecystitis; diffuse bronchopneumonia and pulmonary edema; hypertrophy of small and medium-sized pulmonary arteries, and marked chronic passive congestion of the liver with moderate periportal fibrosis.

Comment.—This patient survived four years after he had first been noted to have a precordial murmur and thrill. Autopsy indicated that these physical signs were due to acquired interventricular septal defects. It is a logical assumption that the septal perforations occurred during the time of the reported episode of coronary thrombosis in July, 1930, four and one-half years before death. Only one patient [3d] among those reported on had a longer survival period, with death occurring 4 years 10 months after perforation of the infarcted septum.

The findings of a thrill and systolic and diastolic murmurs at the apex led to a clinical diagnosis of rheumatic heart disease. This recalls the similar experience of Gross and Schwartz,[5] whose patient was considered clinically to have rheumatic mitral stenosis on the basis of an apical thrill, a questionable apical presystolic murmur, a diffuse systolic murmur, and a loud second pulmonic sound.

5. Gross, H., and Schwartz, S. P.: A Case of Acquired Interventricular Septal Defect Associated with Long-Standing Congestive Heart Failure, Am. Heart J. **11**:626-630, 1936.

The occurrence of systolic and diastolic murmurs in the presence of a ventricular aneurysm, as in this case, was reported in 1885 by Paul,[6] who correlated the presence of these murmurs with an aneurysm found at necropsy. This observation has been confirmed and elaborated by others.[7] In 1896 Remlinger [7a] made a correct diagnosis during the life of his patient, basing his diagnosis on the hearing of systolic and diastolic murmurs 2 cm. above and lateral to the xiphoid process, a localization stressed by Paul. Kasem-Beck,[7b] who intra vitam misinterpreted the diastolic murmur as a sign of mitral stenosis, as did the observers in our case, pointed out a presystolic accentuation of the diastolic murmur due to left ventricular aneurysm. Recently, Scherf and Brooks [7c] analyzed three such cases of cardiac aneurysm due to myocardial infarction evidencing both systolic and diastolic apical murmurs. They differentiated this diastolic murmur from that due to aortic regurgitation by means of stethograms, the vibrations of which revealed presystolic accentuation in contradistinction to the maximum intensity in early diastole in aortic insufficiency. The presystolic murmur noted by Gross and Schwartz [5] in a patient subsequently proved to have a rupture of the interventricular septum but no actual aneurysm may have had its origin in a dynamic aneurysm produced by the extreme left ventricular apical thinning.

Thus, it is seen that a diastolic murmur appearing in a case of recent myocardial infarction may have its origin in a ventricular aneurysm (as well as in rupture of a papillary muscle, about which more will be said later in this paper).

CASE 2.—M. G., a 49-year-old white woman, was admitted to the Beth Israel Hospital on Jan. 27, 1949, complaining of severe chest pain. One hour prior to admission, while walking, she experienced sudden onset of intense, pressing, persistent, substernal pain radiating down both arms and penetrating to the back. This was accompanied with cyanosis, dyspnea, weakness, and nausea.

The patient had known of her hypertension for about five years, with the systolic pressure attaining levels at times above 200 mm. Hg. For several years she had noted dyspnea with moderate exertion and had three-pillow orthopnea. Slight swelling of the ankles had been present for about three months. During a previous admission to the Beth Israel Hospital in 1944 for epithelial ingrowth of the right eye following cataract extraction at another hospital, the patient had had a blood-pressure recording of 134/92, left axis deviation on the electrocardiogram, and no demonstrable cardiac enlargement on routine roentgenogram of the chest. During this admission in 1944 her right eye was enucleated. Additional past history included pneumonia in 1920, 1928, and 1944, and thrombophlebitis of the right leg in 1935.

Physical examination on her admission to the hospital showed an obese, restless, moderately cyanotic woman complaining of substernal pain. The temperature was 99 F.; respirations were 32 per minute; the pulse rate was 94 per minute, and the blood pressure was 220/130. The right orbit contained a glass prosthesis; the left pupil was miotic as a result of morphine administration, and the fundus could not be seen. Coarse, moist rales were heard at both lung bases posteriorly. The point of maximum impulse of the heart was palpable in the fifth left intercostal space at the midclavicular line. The cardiac sounds were of fair quality. The rhythm was regular. There were no thrills or murmurs. The second aortic sound was louder than the second pulmonic sound. The liver was not palpable. There was ankle edema (1+).

The electrocardiogram on admission showed a prominent Q wave and elevation of the S-T segment in Lead CF4, compatible with a diagnosis of acute anterior wall myocardial infarction. Results of urinalysis were normal. The hemoglobin concentration was 13 gm. per 100 cc.; the white blood cell count was 13,800 per cubic millimeter, with a normal differential count. The erythrocyte sedimentation rate (Westergren) was 12 mm. per hour.

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6. Paul, C.: Anévrysme du coeur, Bull. et mém. Soc. méd. hôp. Paris, ser. 3 **2**:83-88, 1885.

7. (*a*) Remlinger, P.: Sclérose de l'artère coronaire antérieure: Dégénérescence consécutive du ventricule gauche; anévrysme du coeur diagnotiqué pendant la vie, Bull. méd., Paris **10**:483-485, 1896. (*b*) Kasem-Beck, A.: Über die diagnostische Bedeutung der präsystolischen Geräusche an der Herzspitze und über einige Symptome der Herzaneurysmen (Ventriculi sinistri), Zentralbl. inn. Med. **18**:137-139, 1897. (*c*) Scherf, D., and Brooks, A. M.: The Murmurs of Cardiac Aneurysm, Am. J. M. Sc. **218**:389-398, 1949.

The patient was placed in an oxygen tent and given morphine sulfate for pain; treatment with bishydroxycoumarin (dicumarol®) was started. Meralluride injection (mercuhydrin® sodium solution), 1 cc., was administered subcutaneously several hours after admission with subsequent diuresis. The following morning the patient was less restless, but complained of a substernal "lump." The blood pressure was 180/120. Examination revealed occasional rales at both lung bases. The heart sounds were of good quality; a blowing Grade 2 systolic murmur, which had not been heard 12 hours previously, was noted at the apex. On Jan. 29, two days after admission, the patient's blood pressure had fallen to 120/76. The heart sounds were fainter, but the apical systolic murmur was slightly louder.

On Jan. 30, auricular flutter developed, with 2:1 block and ventricular rate of 160. The blood pressure fell to 80/60. The patient was apprehensive, cyanotic, and covered with cold perspiration. The heart sounds were distant, but the systolic murmur had become louder and harsher, most prominent in the fifth left intercostal space at the midclavicular line and transmitted over the entire precordium. In view of the increasing intensity of the murmur, which had not been present on admission, it was suggested at this time that perforation of the interventricular septum or rupture of a papillary muscle had occurred. The patient received quinidine and digitalis for her arrhythmia. The auricular rate slowed, and a basic 3:1 block, with occasional 2:1 block, developed. Auricular flutter persisted for two days until the resumption of the regular sinus rhythm. The blood pressure rose from shock levels to 120/90.

The patient's condition steadily worsened. The erythrocyte sedimentation rate on Feb. 1, five days after admission, had risen to 58 mm. per hour. Electrocardiograms showed left ventricular hypertrophy and characteristic serial changes of anterior myocardial infarction.

On Feb. 11, the 16th hospital day, a systolic thrill was noted for the first time in the third and fourth intercostal spaces to the left of the sternum. In addition, the second pulmonic sound had become accentuated, while the second aortic sound was faint. These findings were considered further evidence of septal perforation.

On Feb. 12, a loud "crunching" sound, independent of respirations and synchronous with systole, was heard at the base of the heart, most prominently to the right of the sternum in the second intercostal space. A bedside roentgenogram of the chest showed extreme congestion of both lungs with consolidation at both bases. There was evidence of moderate cardiac enlargement. The "crunch" gradually disappeared over a period of three days.

Nine days before her death, on Feb. 16, the patient was moderately icteric. The liver, which had not been previously palpable, was felt 2 fingerbreadths below the right costal margin. Dyspnea, apprehension, and extreme restlessness increased. Icterus persisted. The blood pressure stayed between 100/80 and 80/60. The systolic murmur and thrill remained prominent. The pulmonic second sound was loud and the aortic second sound very soft. On Feb. 25, the 30th hospital day, the patient suddenly died.

Autopsy Observations.—At autopsy, the enlarged heart weighed 405 gm. The pericardial surfaces were smooth; the apex was formed by both ventricles. The epicardial surface of the anterior wall just above the apex, over an area measuring 5 by 4 cm., was a mottled red-purple and felt thinner than the rest of the heart. The anterior descending artery bisected this area. The right atrium appeared normal; the foramen ovale was closed. The tricuspid valve was not unusual. Close to the apex of the right ventricle a defect in the interventricular septum measuring 2 by 1 cm. formed a wide communication between the ventricles. The right ventricle elsewhere was moderately thick, measuring 0.4 cm. The pulmonic valve, pulmonary artery, left atrium, and mitral valve were not unusual. The left ventricular myocardium was firm and pink-red and measured 1.7 cm. in thickness. The coronary arteries, except as noted below, were moderately atherosclerotic, but not narrowed at any point. No thrombus was found in any major branch. The anterior descending artery was patent and thin-walled through the mottled area to the apex. Three centimeters from its origin a septal branch arose from the anterior descending artery. For about 5 cm. this branch was wide and free from atheroma. At this point in its intramyocardial course, the vessel was suddenly narrowed by an eccentric, bright yellow atheroma. The septal defect briefly mentioned above was situated in the center of a roughly circular, thin portion of the septum about 3.5 cm. in diameter (Fig. 2). The endocardium in this area was in places thick, opaque, and red-brown. In other parts the underlying tissue could be seen through the endocardium; it appeared yellow-brown. These changes extended from the

Fig. 2 (Case 2).—Defect measuring 2 by 1 cm. in lower portion of septum is viewed from left ventricular side. Edges of perforation are smooth, and surrounding endocardium is thickened and opaque. Left ventricle is hypertrophied.

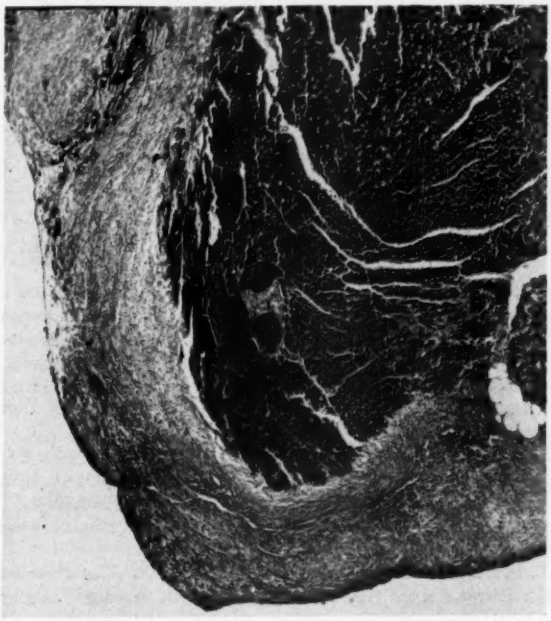

Fig. 3 (Case 2).—Section through edge of perforation. Centrally are seen necrotic muscle fibers of septum. They are surrounded by thick young fibrous tissue which has grown around edge of perforation. Masson trichrome stain; × 42.

septum to the anterior walls of both ventricles and, to less extent, to the posterior walls. At the periphery of the circular area described, the muscle was of normal thickness, but very rapidly, as the defect was approached, the wall became thin, so that the septum for 1 cm. on each side of the defect was about 2 mm. thick. The edges of the defect were rounded and covered by gray endocardium, in some places 1 mm. thick. Horizontal sections through the interventricular septum in the region of the defect showed a variegated yellow, green, and dark red appearance of the myocardium.

Microscopic sections disclosed extensive infarction of the interventricular septum with granulating scar and areas of fresh necrosis and hemorrhage (Fig. 3). Sections of the septal artery described in the gross observations showed marked sporadic narrowing, with severe reduction of the lumen at one point.

Other findings included severe chronic passive congestion of the lungs and liver, with organizing bronchopneumonia, hypertrophy of small pulmonary arteries, and central necrosis of the liver.

Comment.—This case is unique in that the major coronary arteries showed only moderate atherosclerosis, with no narrowing of the lumen. However, an anomalous branch arising from the left anterior descending coronary artery to supply the interventricular septum was markedly sclerotic and its lumen extremely narrowed. The infarction, necrosis, and perforation of the septum can be ascribed to the severe reduction in its blood supply as a result of the atherosclerotic narrowing of this septal branch. A large septal vessel is found regularly in the heart of the dog and pig.[8] Ligation of this vessel in dogs produces septal infarction.[9] Spalteholz,[10] in his monograph on coronary circulation, cites Vieussens as having described in 1715 a septal artery in man, calling it the *artère coronaire intérieure.* There have been other reports of the occurrence of such a vessel in man.[11] Schlesinger and Zoll,[8c] in their large series of injected and dissected human hearts, rarely found such a single large septal vessel. More commonly, a brush of septal branches of various sizes was noted leaving the left anterior descending artery at various levels. No previous case of septal perforation secondary to occlusion of a septal artery has been reported.

The patient showed clinical evidence of pulmonary hypertension with accentuation of the pulmonic second sound. Increased dulness to percussion in the second left intercostal space and sounds resembling a friction rub in this region may be produced by a dilatation of the pulmonary artery.[12] Even though no pulmonary embolus was found at autopsy, a sudden dilatation of the pulmonary artery possibly was the cause of the loud "crunching" sound heard at the base of the heart (but maximally to the *right* of the sternum) late in the course of the patient's illness.

GENERAL COMMENT

Perforation of the interventricular septum is characterized by the appearance of a prominent precordial systolic murmur and thrill in a patient with acute myocardial infarction. The murmur and thrill are usually most pronounced in the fourth and fifth intercostal spaces to the left of the sternum. The murmur is commonly

8. (*a*) Haas, G.: Ueber die Gefässversorgung des Reizleitungssystems des Herzens, Anat. Hefte **43**:629-658, 1911. (*b*) Moore, R. A.: Coronary Arteries of the Dog, Am. Heart J. **5**:743-749, 1930. (*c*) Schlesinger, M. J., and Zoll, P. M.: Incidence and Localization of Coronary Artery Occlusions, Arch. Path. **32**:178-188 (Aug.) 1941. (*d*) Wilson, F. N.; Hill, I. G. W., and Johnston, F. D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction: I. Septal Infarcts and the Origin of the Preliminary Deflections of the Canine Levocardiogram, Am. Heart J. **9**:596-615, 1934.

9. Wilson and others.[8d] Barton, E. M.: Experimental Infarction of the Interventricular Septum of the Heart in the Dog, Proc. Soc. Exper. Biol. & Med. **30**:15-16, 1932.

10. Spalteholz, W.: Die Arterien der Herzwand, Leipzig, S. Hirzel, 1924.

11. Spalteholz.[10] Piquand, G.: Recherches sur l'anatomie des vaissaux sanguins du coeur, J. anat. et physiol. **46**:310-340, 1910.

12. White, P. D.: Heart Disease, ed. 3, New York, The Macmillan Company, 1948, p. 460. Friedberg, C. K.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1950, p. 876.

loud and harsh and may be widely transmitted, even to the back and epigastrium.[13] It often remains prominent despite progressive weakening of the cardiac sounds. As a result of increased pulmonary artery pressure, the pulmonic second sound becomes accentuated, while the aortic second sound is weak or absent. With a large septal defect, a diastolic murmur may also be present at the apex,[14] but, as has already been pointed out, this murmur may be ascribed to the formation of an aneurysm. Occasionally the development of circulatory collapse, with absence of murmur and/or thrill, makes it impossible to diagnose the septal perforation.

Edmondson and Hoxie,[3c] whose 13 cases of septal perforation represent the largest single series, observed that cardiac rupture is most likely to occur in those patients with persistent hypertension after infarction. Perforation almost always takes place within seven days of the onset of myocardial infarction. The immediate prognosis is usually that of the underlying infarction, which must be considered extensive to bring about perforation of the normally richly vascular interventricular septum. Few patients live longer than one month following the perforation. Of the 36 cases reported prior to the presentation by Wood and Livezey [3d] of a patient who survived almost five years, only 7 were believed to have lived more than a month and none was known to have lived as long as a year. Case 1 of the present paper represents the second longest recorded survival. Those patients who live beyond the immediate episode exhibit increasing congestive failure, predominantly right-sided, with cyanosis, hepatomegaly, peripheral edema, and, at times, ascites.

The electrocardiogram shows changes characteristic of acute myocardial infarction. Auriculoventricular conduction defects are seldom encountered, since the perforation usually occurs in the lower portion of the septum. Ford's [3r] patient, with perforation in the posterosuperior segment of the septum extending to the membranous space, showed second-degree heart block. Fowler and Failey [3n] reported the development of interference-dissociation in one case. Patients who survive the immediate episode may display right axis deviation,[15] right ventricular strain, and, in several including our first patient, right bundle branch block.[16]

At autopsy, complete occlusion of one of the major coronary arteries, most frequently the left anterior descending artery, is the usual finding, with marked arteriosclerotic narrowing of the other coronary arteries. Infarction with perforation of the septum as a result of extreme narrowing of an unusual septal branch of the left anterior descending artery, as occurred in Case 2, is unique. The infarction usually involves the lower portion of the interventricular septum and the adjacent anterior or posterior wall of the ventricles, and perforation occurs in the area of infarction and necrosis. As a rule, there is a single perforation, varying from pinhead size to several centimeters in diameter, but multiple defects are seen at times. Since perforation commonly takes place in the lower portion of the septum, it differs from the usual congenital defect (*maladie de Roger*), which lies high up near the base of the septum.

13. Sager.[1] Leonard and Daniels.[3a] Lian and others.[3l]

14. Gross and Schwartz.[5] Brunn, F.: Zur Diagnostik der erworbenem Rupture der Kammerscheidewand des Herzens, Wien. Arch. inn. Med. **6**:533-544, 1923. Moolten, S. E.: Prolonged Survival After Perforation of the Infarcted Interventricular Septum in Coronary Arterial Disease, Arch. Int. Med. **69**:108-116 (Jan.) 1942.

15. Weber.[2] Diaz-Rivera and Miller.[3m]

16. Wood and Livezey.[3d] Stern, N. S.: Rupture of the Interventricular Septum: Case Report, Memphis M. J. **11**:35-36, 1936.

The condition most difficult to differentiate from septal perforation is the even less common rupture of an infarcted papillary muscle. Askey [17] has stressed the absence of a thrill in rupture of a papillary muscle, whereas in at least one-half of all cases of septal perforation a systolic thrill has been palpated. The murmurs associated with rupture of a papillary muscle are frequently bizarre, at times resembling a "to-and-fro loud noise" [18] or simulating a friction rub. They are most intense at the apex, whereas the murmur in septal perforation is usually maximal along the left border of the sternum. A diastolic murmur is commoner in papillary muscle rupture. Although one of Askey's patients survived six months, papillary muscle rupture is generally more catastrophic, with sudden collapse and death within several hours. Pulmonary edema is the predominant feature in those patients who live beyond the immediate episode, while survivors of septal perforation show mainly right-sided heart failure with venous and hepatic congestion.

SUMMARY

Reports on two patients with perforation of the interventricular septum in acute myocardial infarction, with postmortem studies, are presented.

The first patient died four and a half years after perforation had occurred, thus representing the second longest recorded survival. The observations on the first patient tend to confirm previous reports of the development of an apical diastolic murmur in the presence of a cardiac aneurysm.

In the second patient, the perforation was diagnosed during life and was secondary to infarction caused by atherosclerotic narrowing of an unusual septal branch of the left anterior descending artery.

Seventy-seven cases of perforation of the infarcted interventricular septum have now been reported. In 29 the diagnosis was made in life. Diagnosis is based on the development of a systolic murmur and thrill, usually most intense in the third and fourth intercostal spaces to the left of the sternum, in a patient with acute myocardial infarction.

17. Askey, J. M.: Spontaneous Rupture of a Papillary Muscle of the Heart, Am. J. Med. **9**:528-539, 1950.

18. Stevenson, R. R., and Turner, W. J.: Rupture of a Papillary Muscle in Heart as a Cause of Sudden Death, Bull. Johns Hopkins Hosp. **57**:235-242, 1935.

SUPERIORITY OF ILIAC OVER STERNAL MARROW ASPIRATION IN RECOVERY OF NEOPLASTIC CELLS

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AND
AMIEL SMELIN, M.D.
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IT WAS indicated by one of us (M. A. R.) in a previous report [1] that aspiration of bone marrow from the iliac crest may at times provide information not obtained from simultaneous aspiration of the sternal marrow in such infiltrative diseases of the hematopoietic system as multiple myeloma, metastatic cancer to bone, and lymphatic leukemia. In these conditions the iliac marrow often appeared to be involved earlier and more frequently than the sternal marrow. Only a few patients with metastatic cancer were included in this previous study of the relative merits of iliac and sternal marrow aspirations.

PRESENT STUDY

The present study is a report on 100 consecutive patients admitted to the Division of Neoplastic Diseases of Montefiore Hospital. Each of these patients had pathologically proved malignant disease with definite evidence of distant metastases. There were 32 patients with cancer of the breast, 18 with genitourinary cancer, 14 with gastrointestinal cancer, 15 with pulmonary neoplasms, 4 with cancer of the thyroid, and 17 with miscellaneous neoplasms, including 6 with sarcomas and 11 with proved metastatic cancer but with the primary site undiscovered.

A total of 64 patients showed definite evidence on roentgenographic study of osseous metastases; the remainder had evidence of visceral and soft-tissue metastases.

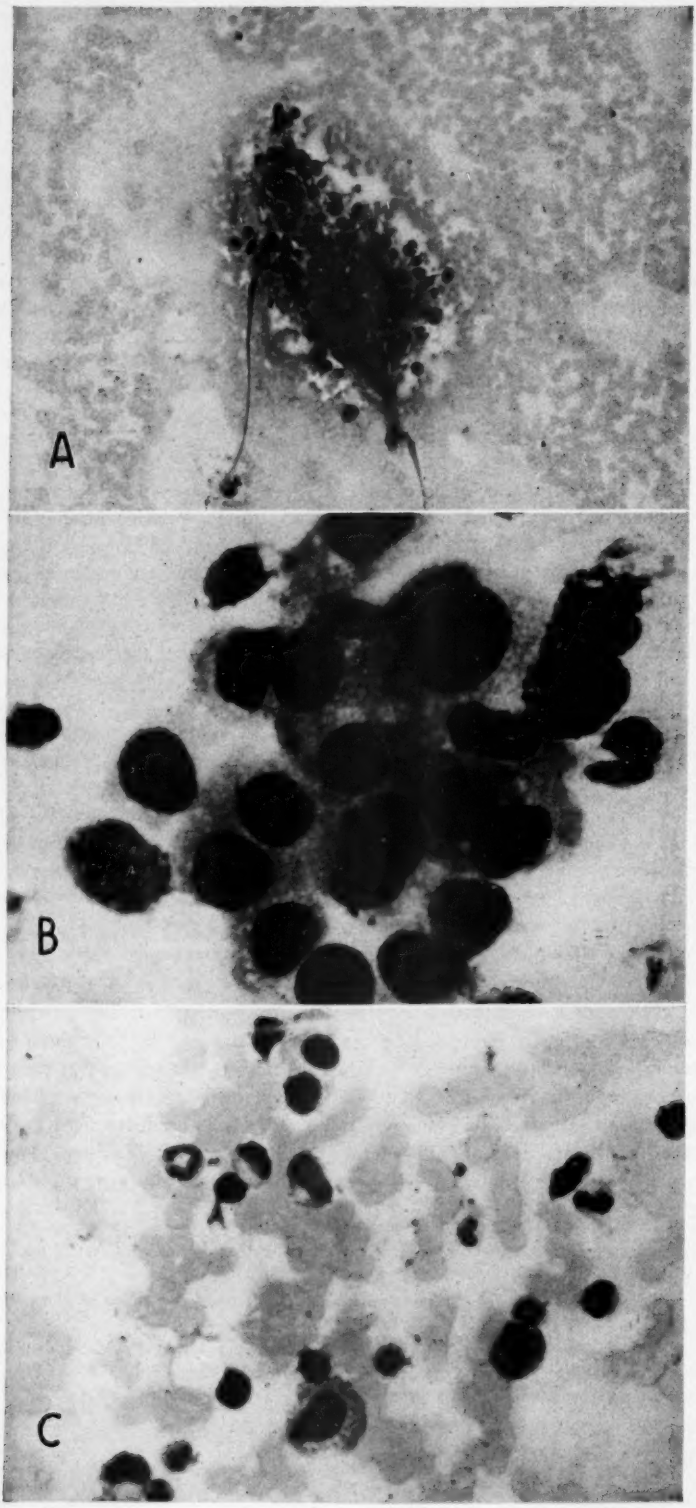
In each patient simultaneous aspiration of the sternal and iliac marrow was performed according to the technique described previously.[2] At least three smears of each aspiration were thoroughly scrutinized before the aspiration was considered to be negative for tumor cells. The cytological characteristics and the criteria for recognizing neoplastic cells in bone marrow smears have been described in detail.[3] In smear preparations, tumor cells generally occur in characteristic clumps; however, they may also occur singly. When present, they are usually grouped along the

From the Division of Neoplastic Diseases, Montefiore Hospital.

1. Rubinstein, M. A.: Aspiration of Bone Marrow from the Iliac Crest, J. A. M. A. **137**:1281, 1948.

2. Rubinstein, M. A.: The Technic and Diagnostic Value of Aspiration of Bone Marrow from the Iliac Crest, Ann. Int. Med. **32**:1095, 1950.

3. Rohr, K., and Hegglin, R.: Tumorzellen im Sternalpunkta: Metastasennachweis maligner Geschwülste im Knochenmark, Deutsches Arch. klin. Med. **179**:61, 1936; Das menschliche Knochenmark, Ed. 2, Stuttgart, Georg Thieme, 1949, pp. 349-356.



(See legends on opposite page)

edges of the smear, especially if the hematopoietic elements of the marrow are greatly reduced or absent. The great frequency of aplastic or hypoplastic bone marrow smears in preparations positive for neoplastic cells has been discussed in an earlier publication.[4]

In a number of cases of metastatic cancer involving the bone marrow, no marrow was obtained on aspiration. Instead a solid mass of tumor tissue was drawn up into the bore of the marrow needle. We made it a practice to smear all such tissue and examine the smears for malignant cells.

RESULTS AND COMMENT

Table 1 summarizes the comparative incidence of malignant cells as observed in the sternal and the iliac marrow. It will be noted that a total of 41 patients in the series of 100 showed neoplastic cells in either the sternal or the iliac marrows, or in both. This high percentage of positive results in our series is quite certainly attributable to the fact that the patients were generally in the *late* stages of metastatic

TABLE 1.—*Results in One Hundred Cases in Which Simultaneous Sternal and Iliac Marrow Aspirations Were Performed*

Primary Site of Tumor	Total No. of Cases	Iliac Marrow Positive; Sternal Marrow Negative	Sternal Marrow Positive; Iliac Marrow Negative	Both Positive	Both Negative
Breast	32	8	3	9	12
Genitourinary tract	18	7	0	2	9
Gastrointestinal tract	14	0	0	1	13
Pulmonary region	15	2	1	2	10
Thyroid	4	0	0	0	4
Miscellaneous (sarcomas; metastatic carcinomas, primary site unknown)	17	5	0	1	11
Total	100	22	4	15	59

malignant disease; more than two-thirds showed roentgenographic evidence of bone metastases. These were mostly terminal cases.

Our incidence of successful recovery of neoplastic cells by means of bone marrow aspiration (41% of cases) is among the highest in the literature.[5] Other investigators have reported incidences ranging from 6%[5b] to 50%.[6] This marked variation in

4. Rubinstein, M. A., and Smelin, A.: Neoplastic Cells in Bone Marrow Aspiration, Acta haemat. **5**:292, 1951.

5. (*a*) Rohr and Hegglin.[3] (*b*) Walther, H. E.: Untersuchungen über Krebsmetastasen: III. Mitteilung, Radiol. clin. **8**:69, 1939. (*c*) Kreyberg, L., and Poppe, E.: Tumour Cells in Sternal Bone Marrow, abstracted, Lancet **1**:593, 1940. (*d*) Stöger, R.: Das Sternalpunkta beim malignen Neoplasma, Deutsche med. Wchnschr. **67**:1389, 1941. (*e*) Francke, E.: Cytologischer Nachweis von Tumorzellen in Markpunktaten, Ztschr. klin. Med. **140**:622, 1941-1942. (*f*) Lanier, P. F.: Sternal Marrow in Patients with Metastatic Cancer, Arch. Int. Med. **84**:891, 1949.

6. Mallet and Casne, cited by Rohr and Hegglin.[3]

EXPLANATION OF FIGURE

Photomicrographs from Patient M. H., with metastatic cancer of breast. *A*, iliac aspiration. Low-power view showing clump of metastatic cells in aplastic marrow. *B*, iliac aspiration. High-power view of neoplastic cells in same smear. *C*, sternal marrow aspiration, showing fair nucleated-cell content. No neoplastic cells were seen.

(See legends on opposite page)

results in various studies is in all probability dependent on the type of patient studied, the degree of malignant invasion present, and the site of aspiration. This premise is well supported by the recent study of Jonsson and Rundles, who carefully selected the site of aspiration to correspond with roentgenographic evidence of malignant bone involvement. They obtained positive findings in 71 (47%) of a series of 152 patients with various types of cancer.[7]

The superiority of the iliac marrow compared with the sternal marrow as the site for aspiration may be seen from Table 1; the sternal marrow was negative for tumor cells in 22 patients in whom the iliac marrow smears were positive. On the other hand, in only four patients were tumor cells present in sternal marrow aspirates and not in those from the iliac marrow. It is interesting to note that these four patients all suffered from thoracic neoplasms: Three had breast carcinoma and one had a bronchogenic cancer. Of the nine patients with genitourinary cancer who showed tumor cells in the iliac marrow, only two had simultaneous sternal marrow aspirations positive for the cells.

The figure compares the iliac crest and sternal marrow smears in a case of cancer of the breast. The iliac marrow is aplastic and contains large clumps of neoplastic cells. The sternal marrow, on the other hand, is normally cellular and contains neither clumps nor individual abnormal cells.

As was discussed briefly in a previous paper,[4] bone marrow aspiration in the search for malignant cells may be a valuable procedure in several different circumstances. First, marrow aspiration may be employed in obscure problem cases as yet undiagnosed; in such cases, the routine employment of marrow puncture will occasionally reveal the unexpected presence of tumor cells, as well as other abnormalities, and thus provide a definite diagnosis. Second, marrow aspiration may provide a means of making a definite cytological diagnosis of cancer in cases in which there is clinical or roentgenologic evidence to suggest such a diagnosis, but no readily accessible site is available for biopsy. Third, this procedure may be employed in cases of known primary malignant growth in order to establish definite evidence of metastatic bone involvement before roentgenographic changes are apparent. Finally, in cases with positive marrow aspirations, a readily available source of tumor cells is present, and they may be obtained by the relatively simple procedure of marrow puncture on repeated occasions. Thus, the effect of various forms of therapy on the individual tumor cells may be judged, the tumor cells being obtained from an easily accessible site with relatively little physical or psychological trauma to the patient.

The findings presented in this paper, namely, the superiority of iliac crest over the sternal marrow as a site for aspiration of tumor cells, suggest that when marrow aspiration is done as part of a diagnostic work-up either in an obscure syndrome or in one suggestive of cancer, or when aspiration is done in an attempt to demonstrate metastatic bone involvement, the procedure of choice is iliac rather than sternal puncture.

Table 2 presents a breakdown of cases according to the presence or absence of roentgenographic evidences of bone metastases. As would be expected, positive aspirations were much more frequent in patients with roentgenographic evidence of bony metastases; of the 64 patients with roentgen findings strongly suggestive

7. Jonsson, U., and Rundles, R. W.: Tumor Metastases in Bone Marrow, Blood **6**:16, 1951.

of metastases in the osseous structures, 35 showed tumor cells in either the sternal or the iliac marrow, or in both. However, it is of interest to note that 6 positive aspirations were obtained in the group of 36 patients with no evidence on roentgenograms of osseous metastases.

TABLE 2.—*Bone Marrow Findings in Cases With and Without Roentgenographic Evidence of Osseous Metastases*

Primary Site of Tumor	Roentgenograms Positive				Roentgenograms Negative			
	Total No. of Cases	Marrow Positive			Total No. of Cases	Marrow Positive		
		Iliac Only	Sternal Only	Both		Iliac Only	Sternal Only	Both
Breast	29	8	3	9	3	0	0	0
Genitourinary tract	9	6	0	2	9	1	0	0
Gastrointestinal tract	4	0	0	1	10	0	0	0
Pulmonary region	8	0	1	1	7	2	0	1
Thyroid	3	0	0	0	1	0	0	0
Miscellaneous (sarcomas; metastatic carcinomas, primary site unknown)	11	3	0	1	6	2	0	0
Total	64	17	4	14	36	5	0	1

CONCLUSIONS

In 100 consecutive patients with *advanced* metastatic malignant disease, neoplastic cells were observed considerably oftener in iliac than in sternal marrow aspirations performed simultaneously. Both sternal and iliac aspirations were positive in 15 patients. Both sternal and iliac aspirations were negative in 59 patients. Iliac aspiration alone was positive in 22 patients. Sternal aspiration alone was positive in four patients.

Patients in whom sternal marrow aspiration alone was positive suffered from either cancer of the breast or cancer of the lung.

Of 36 patients with no roentgenographic evidence of osseous metastases, 6 showed tumor cells in smears of marrow aspirates. All six patients had positive iliac marrow aspirations; only one had a concomitant positive sternal marrow aspiration.

As a result of these findings, it is suggested that the iliac marrow is superior to the sternal marrow as a site for aspiration of tumor cells.

Dr. Daniel Laszlo, Chief, Division of Neoplastic Diseases, Montefiore Hospital, New York, assisted us in this study.

TUBERCULOSIS AND THE SICKLE-CELL TRAIT

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TUBERCULOSIS in the Negro race differs from tuberculosis in the white race. In the Negro [1] it is more frequently an acute disease and has a higher mortality rate. This difference may be due to environmental factors or to racial factors of resistance. Economic and social factors may be important in some cases, but under conditions in which such factors are equal in both races the Negro race continues to show a higher mortality than does the white race.[2] Racial resistance to the disease must, therefore, be important in determining the type of tuberculosis which is prone to develop in the Negro.

Sicklemia (the sickle-cell trait) is found in a significant number of Negroes, 7.25% of Negroes in the United States.[3] This is a racial trait which is almost entirely limited to the Negro. Therefore, it was thought that it would be worth while to determine whether there is any relation between sicklemia and pulmonary tuberculosis in the Negro.

Most authors feel that the sickling trait has little clinical significance.[4] This impression may be due to a lack of adequate investigation. The relation of sicklemia to various disease manifestations cannot be readily recognized because this trait does not give rise to any overt symptoms or signs per se. In order to uncover any clinical significance to the trait, it is necessary to test for it.

In the past, few persons have considered the possibility that sicklemia might influence another disease process, such as tuberculosis, the progress of which may depend on blood supply and hematological and vascular phenomena. Yet it has been recognized that active sickle-cell anemia predisposes the patient to tuberculosis. A previous study by Weiss and Waife [5] corroborated this on a statistical basis.

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1. Bogen, E.: Racial Susceptibility to Tuberculosis, Am. Rev. Tuberc. **24**:522 (Nov.) 1931. Israel, H. L., and Payne, H. M.: Tuberculosis in the Negro: Clinical and Roentgenological Characteristics, ibid. **41**:188 (Feb.) 1940.

2. West, J. B.: An Inquiry into the Importance of the Racial Factor in the Epidemiology of Tuberculosis, Am. Rev. Tuberc. (Supp.) **41**:114, 1940.

3. Margolies, M. P.: The Incidence of Sickling, Am. J. M. Sc. **221**:270 (March) 1951.

4. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942, p. 467. Sturgis, C. C.: Hematology, Springfield, Ill., Charles C Thomas, Publisher, 1948, p. 329.

5. Weiss, W., and Waife, S. O.: Sickle Cell Anemia and Tuberculosis, Am. Rev. Tuberc., to be published.

In some respects the difference between sickle-cell anemia and the sickling trait is a quantitative rather than a qualitative one.[6] Therefore, it is reasonable to suppose that sicklemia may also predispose to tuberculosis and influence the latter disease to some extent.

There are two studies of the sickling trait in relation to tuberculosis, but they conflict in conclusions. At Sea View Hospital, Staten Island, N. Y., 77 tuberculous Negroes were tested for the sickling trait, and an incidence of 5.2% was found.[7] However, no mention was made of the type of tuberculosis in patients with the trait as compared with those not showing it. Furthermore, Sea View Hospital is a municipal sanatorium rather than a general hospital, and the type of tuberculous patient admitted to a sanatorium may differ from the type of patient admitted to a large municipal general hospital such as ours. This may explain the normal incidence of sicklemia found at Sea View Hospital and the increased incidence at the Philadelphia General Hospital.

Herrera Cabral[8] recently mentioned six patients with the sickling trait, four of whom had acute tuberculosis. None of these responded to therapy. The author concluded that the frequent presence of sickle cells in the blood was the main factor in the type of tuberculosis which tends to develop in Negroes. Obviously this investigation was inadequate in numbers to warrant such a conclusion.

It was felt that this problem justified a more thorough investigation. It is the purpose of this paper to report our findings at the Philadelphia General Hospital in a series of patients which is large enough to warrant statistical analysis.

METHOD

The sickling test used in this investigation[9] consisted of mixing a drop of blood (fingertip) with a drop of fresh sodium metabisulfite[10] solution on a glass slide. The mixture was covered with a glass cover slip; the preparation was sealed with petroleum jelly and allowed to stand at room temperature. This slide was examined with the microscope the following morning as a matter of convenience. Those slides in which sickle cells were rare were read as negative. Those in which most of the red cells were sickled were read as positive.

The test was carried out on 150 tuberculous Negroes at random in the Department of Chronic Diseases of the Chest. For a control series, the test was done on 153 consecutive Negroes admitted to other hospital departments as they came through the photofluorographic unit in the receiving ward for miniature chest roentgenograms. Three persons who later proved to have tuberculosis were excluded, leaving 150 patients in the control series.

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6. (*a*) Murphy, R. C., Jr., and Shapiro, S.: The Pathology of Sickle Cell Disease, Ann. Int. Med. **23**:376 (Sept.) 1945. (*b*) Lange, R. D.; Minnich, V., and Moore, C. V.: Effect of Oxygen Tension and of pH on the Sickling and Mechanical Fragility of Erythrocytes from Patients with Sickle Cell Anemia and the Sickle Cell Trait, J. Lab. & Clin. Med. **37**:789 (May) 1951.

7. Dolgopol, V. B., and Stitt, R. H.: The Sickle-Cell Phenomenon in Tuberculosis Patients, Am. Rev. Tuberc. **19**:454 (April) 1929.

8. Herrera Cabral, J. M.: Sickle Cell Anemia and Tuberculosis, Rev. méd. Dominicana **5**:265 (Oct.-Dec.) 1950.

9. Daland, G. A., and Castle, W. B.: A Simple and Rapid Method for Demonstrating Sickling of the Red Blood Cells: The Use of Reducing Agents, J. Lab. & Clin. Med. **33**:1082 (Sept.) 1948.

10. This solution was made up daily by dissolving a 3-grain (0.19-gm.) tablet of sodium metabisulfite in 10 cc. of water. The tablets were supplied by Dr. Woodson C. Young, of the Lilly Research Laboratories, Eli Lilly & Company, Indianapolis 6.

RESULTS

Of 150 tuberculous Negroes, 19, or 12.6%, were found to have the sickling trait. Of 150 nontuberculous Negroes, 8, or 5.3%, were found to have the trait. The difference between these two groups is statistically significant ($P < 0.05$).

In the group of tuberculous Negroes, the type of pulmonary tuberculosis in those with the sickling trait was compared with the type found in those without the trait. It was noted that roentgenographically 14 of the 19 with the trait had an exudative [11] type of tuberculosis on admission to the hospital. This is an incidence of 74%. There were, in contrast, 50 with exudative tuberculosis among the 131 without the trait, an incidence of 38%. Therefore, exudative tuberculosis occurred almost twice as frequently among Negroes with the sickling trait as among those without the trait. This difference was statistically highly significant ($P < 0.01$). Conversely, among the 64 with exudative tuberculosis in the total series of 150

Characteristics of Tuberculous Negroes with the Sickle-Cell Trait Compared with Those Without the Sickle-Cell Trait

	With Sickle-Cell Trait			Without Sickle-Cell Trait		
Characteristic	All Patients	Patients with Exudative Tuberculosis	Patients with Nonexudative Tuberculosis	All Patients	Patients with Exudative Tuberculosis	Patients with Nonexudative Tuberculosis
No. of patients	19	14	5	131	50	81
Average age, yr.	35	33	41	36	36	36
Per cent males	42	43	40	42	44	41
Average hemoglobin concentration, gm./100 cc.	11.6	11.6	11.6	11.3	11.2	11.3
Average duration of tuberculous symptoms prior to admission, mo.	4.7	4.6	4.8	8.1	5.5	9.8
Per cent with fever on admission	95	93	100	77	92	68

tuberculous Negroes, 14, or 22%, had the sickling trait. Thus, given a case of exudative tuberculosis in a Negro, there are 22 chances in 100 that the patient has the sickling trait. This figure is four times as great as that for the incidence of the sickling trait among nontuberculous Negroes admitted to a large general hospital (5.3%). Figures 1 to 4 illustrate the types of roentgenographic lesions which were classified as exudative pulmonary tuberculosis.

Two of the patients showing the sickling trait had miliary tuberculosis, while none of those without the trait had miliary disease. These numbers are too small to warrant any conclusions.

In one of our patients with the sickling trait a pneumonectomy had been performed. His chest roentgenogram is illustrated in Figure 4. Microscopic sections of the lung showed that all vessels in the tuberculous tissue were packed with sickled red cells (Fig. 5). Unfortunately, there were no sections of normal lung tissue available from this patient for comparison.

11. The term "exudative tuberculosis" is used in this study to mean the presence of a large area of homogeneous heavy density (consolidation) or extensive patchy, but markedly confluent, soft fluffy densities throughout at least an entire lobe on the posteroanterior roentgenogram of the chest. Primary tuberculosis is also classified as exudative tuberculosis.

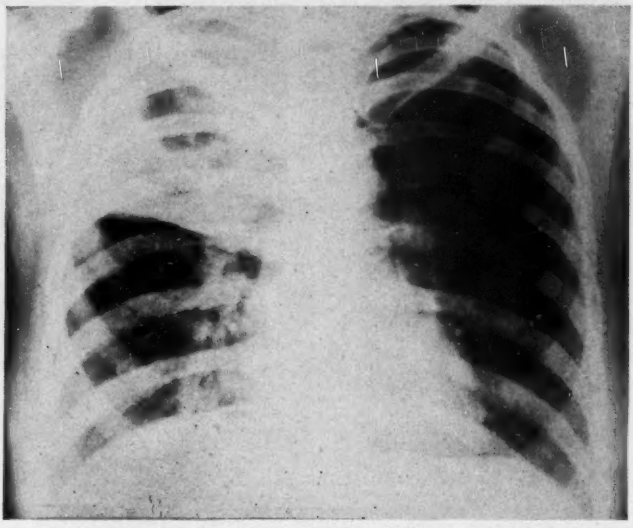

Fig. 1.—Chest roentgenogram of patient with exudative pulmonary tuberculosis, consisting of consolidation of right upper lobe which has progressed to cavitation.

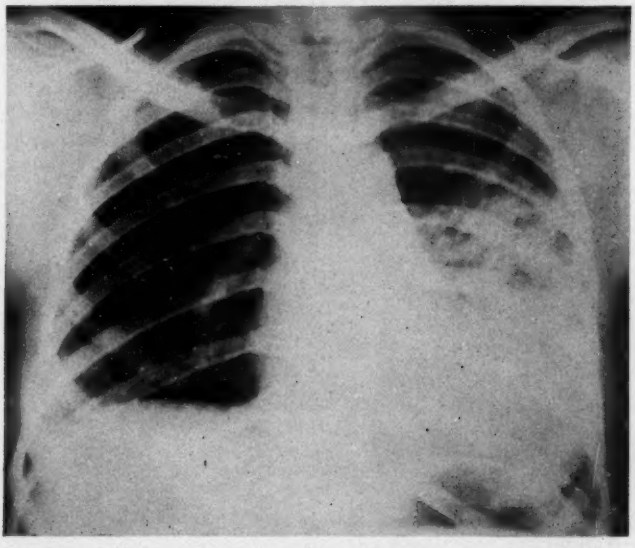

Fig. 2.—Chest roentgenogram of patient with exudative pulmonary tuberculosis in left lower lobe, consisting of patchy, but markedly confluent, soft fluffy densities.

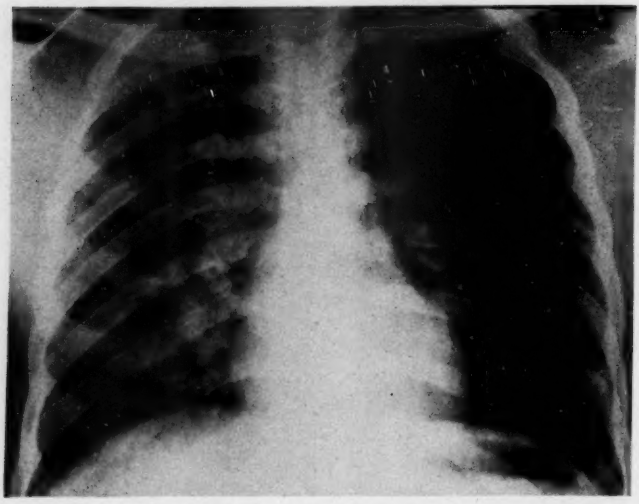

Fig. 3.—Chest roentgenogram of patient with exudative pulmonary tuberculosis, primary in type, consisting of soft fluffy peripheral infiltration and hilar lymphadenopathy.

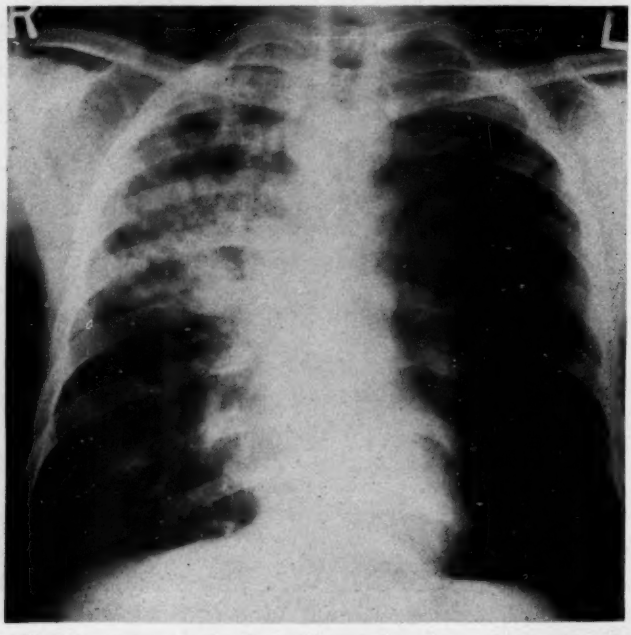

Fig. 4.—Chest roentgenogram of patient with exudative pulmonary tuberculosis in the right upper lobe, consisting of patchy, but markedly confluent, soft fluffy densities.

Tuberculous patients with the trait were compared with tuberculous patients not showing the trait with respect to the hemoglobin concentration, the temperature on admission, and the known duration of tuberculosis prior to hospitalization, as well as age and sex. The findings are summarized in the table. Patients with and without the trait were further broken down into those with exudative tuberculosis and those with nonexudative tuberculosis. This breakdown among the group with

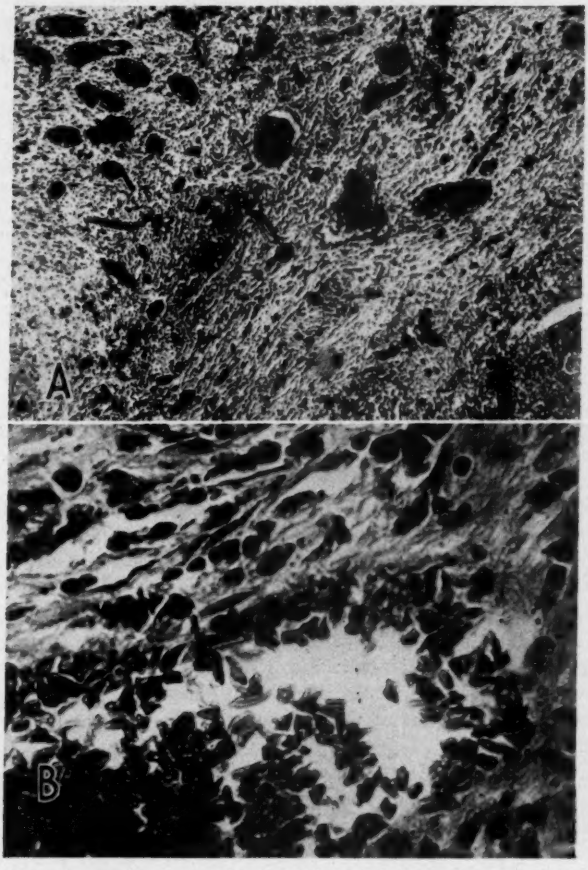

Fig. 5.—Photomicrographs of a section from the resected lung of the patient whose chest roentgenogram is illustrated in Figure 4. *A*, tuberculous tissue with numerous markedly engorged blood vessels; × 184. *B*, note sickled red cells in engorged capillaries; × 736.

the sickling trait was of limited value because the number of patients was small. However, most of those showing the trait had exudative tuberculosis. Therefore, it is of value to compare the characteristics of all tuberculous patients having the trait with the characteristics of those without the trait having exudative tuberculosis and those without the trait having nonexudative tuberculosis.

It is apparent that there were no age or sex differences between these groups. Likewise, there were no differences in hemoglobin values. However, with respect to the duration of tuberculosis symptoms prior to admission and the percentage of patients with fever on admission, the patients with the sickling trait resembled only those without the trait who had exudative tuberculosis. This is undoubtedly due to the fact that most of the patients showing the trait had an exudative type of pulmonary tuberculosis. The similarity in hemoglobin values among all groups emphasizes the point that the patient whose cells showed sickling had the sickle-cell trait rather than sickle-cell anemia.

COMMENT

It is apparent from the results of this study that there is some relation between the sickling trait and tuberculosis. It is possible that this relation is indirect, that the sickling trait is associated with some other factor that influences the response of the patient to tuberculous infection. However, it is also possible that sicklemia may have a direct effect in tuberculosis, for, despite the fact that this trait is commonly dismissed as being of no clinical significance, it may well be that sicklemia produces minor obstructive vascular phenomena [12] which are important in certain disease processes under certain conditions.

Indeed, it is now acknowledged that sicklemia differs from sickle-cell anemia only in degree rather than in kind with respect to the effect of oxygen tension and pH. Further, it may be extremely difficult to distinguish the sickle-cell trait from active sickle-cell disease. Green and Conley [13] recently reported four cases in which important manifestations of sickle-cell disease occurred without persistent anemia of jaundice.

Sickling is precipitated by low oxygen tensions and is enhanced by low pH in the red cell environment.[14] In general, to produce sickling, oxygen tension in the blood of persons with the trait must be lower than that in the blood of patients with sickle-cell anemia. However, there is no clear-cut demarcation and there is some overlap. Trait red cells from some persons may sickle at the higher oxygen tensions which will produce sickling of red cells from patients with sickle-cell anemia. Therefore, it is probable that sickling may occur under appropriate conditions in the vessels of some Negroes with the sickling trait, as well as in those of Negroes with the full-blown picture of sickle-cell anemia. If this is true, then the sickling trait is more important than the anemia in a Negro population, because it is far commoner.

We have two findings in this investigation to explain: the increased incidence of sickling trait in tuberculous Negroes and the increased incidence of exudative tuberculosis in tuberculous Negroes exhibiting the sickling trait.

The higher incidence of sicklemia in tuberculous Negroes as compared with the general Negro population may be due to a possible effect of tuberculosis, in that this infection may cause the sickling trait to appear where it did not exist before. This is unlikely because the trait is acknowledged to be an inherited characteristic

12. Henderson, A. B.: Sickle Cell Disease: Studies on "in Vivo" Sickling and the Effect of Certain Pharmacological Agents, Am. J. M. Sc. **221**:628 (June) 1951.

13. Green, T. W., and Conley, C. L.: Occurrence of Symptoms of Sickle Cell Disease in the Absence of Persistent Anemia, Ann. Int. Med. **34**:849 (April) 1951.

14. Lange and others.[6b] Daland and Castle.[9]

which acts as a Mendelian dominant.[15] It is much more likely that persons with the sickling trait have clinical tuberculosis oftener than do Negroes who are without the trait, and, therefore, more persons showing the trait appear among a tuberculous Negro population.

The increased incidence of exudative tuberculosis in persons with the sickling trait must also be explained. It may represent an extension of the original small area of lobular tuberculous pneumonia which occurs as the result of the initial tuberculous infection.

Conditions in the mixed venous blood which enters the lungs for aeration are most suitable to production of sickling of the red cells because the oxygen tension approaches the low levels required to precipitate sickling (below 45 mm. Hg). The pH is also low, and this favors sickling. We might consider the following hypothesis: The presence of sickle cells in the pulmonary arterial blood may tend to obstruct the flow of blood through the capillaries at least at the arterial end of the vessel, because of the pointed shape of the red cells. Blood flow then would be sluggish until the red cells approach the venous end of the capillary. On exposure to alveolar oxygen, many of the sickle cells then should resume a normal shape. However, because of the relative obstruction at the arterial end of the capillary, blood flow through the capillary may be slowed and, therefore, less oxygen is taken up from the alveolar air per unit of time. This should leave a greater amount of oxygen available in the alveolar air.

The tubercle bacillus is an aerobe and, within certain limits, grows better in atmospheres of higher oxygen tension.[16] Therefore, when the bacillus invades an alveolus from which oxygen is removed at a slower rate, we would expect that the bacillus could grow better and multiply faster. Such a state of affairs would be reproduced in other alveoli as tubercle bacilli spread to them. Thus, the lobular pneumonia of the initial tuberculous infection would assume greater proportions in a person with the sickling trait and would lead to an increased incidence of clinical tuberculosis, particularly exudative tuberculosis, in these persons.

There is little or no evidence to support such a hypothesis as has been outlined above. It was promulgated in a previous paper on the relation between active sickle-cell anemia and tuberculosis.[5] Whether this hypothesis is tenable or not will depend on further investigation.

Lurie [17] feels that tissue resistance is more important than oxygen tension to the bacillus in determining the outcome of tuberculous infection. It may be more likely that the conditions existing in the area of inflammatory reaction precipitate sickling in the vessels contained in the tuberculous tissue. We would expect this to be so because not only is the oxygen tension low in the inflammatory tissues but the pH

15. Watson, J.; Stahman, A. W., and Bilello, F. P.: The Significance of the Paucity of Sickle Cells in Newborn Negro Infants, Am. J. M. Sc. **215**:419 (April) 1948.

16. Rich, A. R., and Follis, R. H., Jr.: The Effect of Low Oxygen Tension upon the Development of Experimental Tuberculosis, Bull. Johns Hopkins Hosp. **71**:345 (Dec.) 1942. Corper, H. J.; Lurie, M. B., and Uyei, N.: The Variability of Localization of Tuberculosis in the Organs of Different Animals: III. The Importance of the Growth of Tubercle Bacilli as Determined by Gaseous Tension, Am. Rev. Tuberc. **15**:65 (Jan.) 1927.

17. Lurie, M. B.: Personal communication to the authors.

is on the acid side.[18] These conditions would tend to obstruct the blood supply to the diseased tissues and so strangle their resistance through the lack of adequate supplies of antibody and nutrients. As a result of lowered tissue resistance, the initial tuberculous infection may progress and so give rise to the higher incidence of clinical tuberculosis, especially exudative tuberculosis, among those exhibiting the sickling trait as compared with Negroes who do not have the trait.

Whatever the explanation may be, it is apparent that the sickling trait has definite clinical significance and is an important factor in the response of some Negroes to tuberculous infection.

CONCLUSIONS

It is shown that the sickling trait is more than twice as common (12.6%) among tuberculous Negroes admitted to a large municipal general hospital as it is among nontuberculous Negroes admitted to the same hospital (5.3%).

It is also shown that exudative tuberculosis is twice as common among tuberculous Negroes with the sickling trait (74%) as it is among tuberculous Negroes without the trait (38%).

The possible explanations for these findings are discussed.

The sickling trait has definite clinical significance and is a factor in the response of some Negroes to tuberculous infection.

Mrs. Sarah Stokes gave technical help. The Department of Laboratories provided pathological material in one case. Dr. Peter Theodos, Dr. William Lampe, Dr. Jack Kirshner, and Dr. Nathan Blumberg gave permission for use of their clinical material.

18. Menkin, V.: Dynamics of Inflammation, New York, The Macmillan Company, 1940, p. 85.

MORPHOLOGIC STUDY OF THE CARDIAC CONDUCTION SYSTEM

VI. The Intrinsic Nervous System of the Heart

D. J. GLOMSET, M.D.
AND
K. R. CROSS, M.D.
DES MOINES, IOWA

MORE THAN a decade ago one of us (D. J. G.) [1] encountered a case of right and a case of left bundle branch block. Being interested in the lesions within the branches of the His bundle, which are supposed to produce the bizarre electrocardiographic complexes characteristic of bundle branch block, he obtained the hearts at necropsy for a study of the blocking lesions.

No difficulty in locating the bundle was anticipated because texts on the heart contain detailed descriptions of the two nodes and the bundle that comprise the so-called conduction system. A meticulous search of the hearts failed to reveal the bundle. This surprising result stimulated the Glomsets [2] to investigate the conduction system in various mammals. Adequate numbers of hearts from man, dog, monkey, horse, sheep, cattle, and swine were examined grossly and microscopically. They concluded that there does not exist in the hearts of any of the mammals examined a sinoatrial node, an atrioventricular node, or an atrioventricular bundle.

In the ungulates, as in the horse, a ventricular bundle is present, which is strikingly like the His bundle described and pictured in various texts as existing in man and dog. The ungulate ventricular bundle consists of altered muscle fibers and nerve elements in the ratio of about 1 : 1. The muscle component originates in the atrioventricular fibrous ring just posterior to the central fibrous body. The nerve component originates in the intrinsic ganglia lying cephalad to the stem of the bundle. In sheep and cattle the muscle fibers first interlace, forming the node of Tarawa; then, on leaving the node, they join the nerve fibers of the bundle and change abruptly to thick, short, binucleated, muscle cylinders—the Purkinje fibers.

From the Departments of Internal Medicine and Pathology, Veterans Administration Hospital.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own work and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Glomset, D. J.: The Structure of the Cardiac Conduction System in Man and Other Mammals, Proc. Inst. Med. Chicago **13**:398, 1940-1941.

2. Glomset, D. J., and Glomset, A. T. A.: A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog and Man: I. The Sino-Atrial Node, Am. Heart J. **20**:389, 1940; II. The Purkinje System, ibid. **20**:677, 1940.

These are arranged in strands, among the nerve fibers, throughout the bundle and the Purkinje networks. The stem of the bundle bifurcates at the lowest point of the fibrous septum, sending a branch to each ventricle. By subdivision, the branches form subendocardial and intramuscular networks.

Glomset and Birge [3] studied the anatomy of the upper part of the interventricular septum and the atrioventricular groove in man and dog. They found that the bundle described by His [4] is a superficial group of muscle fibers lying subendocardially in the upper part of the left side of the ventricular septum. In the photograph shown by His the bundle terminates in the aortic part of the atrioventricular fibrous ring.

The anatomic basis for the His bundle described by Tawara [5] and many others is an ordinary muscle fasciculus, "the ridge fasciculus," originating in the same

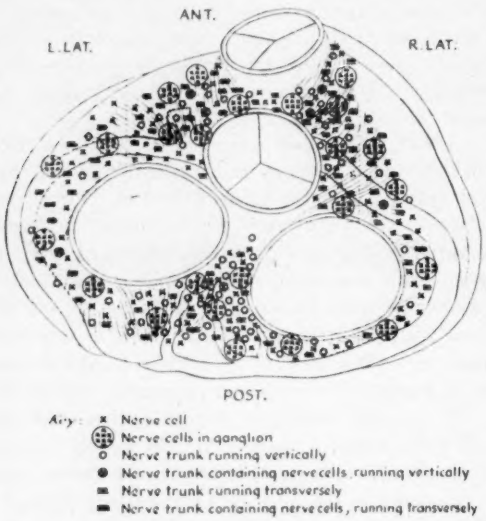

Fig. 1.—Schematic drawing of nerve elements in auriculoventricular groove in man. (After Glomset and Birge.[3])

locality as does the muscular component of the ungulate bundle. It runs forward on top of the septum into the right ventricle, does not send a branch to the left ventricle or subdivide into Purkinje networks, and is tinctorially and structurally identical to neighboring fasciculi.

In the atrioventricular sulcus (Fig. 1), Glomset and Birge found numerous nerve trunks and nerve cells occurring either singly or as large and small ganglia.

3. Glomset, D. J., and Birge, R. F.: A Morphologic Study of the Cardiac Conduction System: IV. The Anatomy of the Upper Part of the Ventricular Septum in Man, Am. Heart J. **29**:526, 1945.

4. His, W., Jr.: Die Thätigkeit des embryonalen Herzens und deren Bedeutung für die Lehre von der Herzbewegung beim Erwachsenen, Arb. med. Klin., Leipzig., 1893, p. 14.

5. Tawara, S.: Das Reizleitungssystem des Säugetierherzens, Jena, C. Fischer, 1906.

The smaller ganglia were often located near or within the nerve trunks. Most of the nerve trunks followed the coronary arteries; some crossed directly from atrium to ventricle.

PRESENT STUDY

Because of the abundance of nerve elements in all hearts examined, we decided to investigate the intrinsic nervous system of the heart to determine, if possible, its relation to impulse formation and conduction. This communication deals with the development of knowledge concerning cardiac conduction, the topography of the cardiac nerve elements, and the nerve endings on muscle cells.

HISTORICAL STUDIES

From Hippocrates to Harvey the "subtle flame" theory of the Father of Medicine sufficed to explain the rhythmic beating of the heart. Between 1616 and 1664 the medical profession became aware of the fact that the impulse producing muscular contraction originates within nerve cells and is transmitted by nerve fibers to working muscles. Willis [6] reasoned that because the heart is muscle it, too, depends for contraction upon the activity of nerves and, thereby, gave birth to the neurogenic theory. However, nearly a hundred years later (1759), Haller,[7] well aware that all hearts are capable of rhythmic contraction after their extrinsic nerve fibers have been severed, but not aware of their intrinsic nervous systems, timidly suggested that impulse formation and transmission in the heart are due to the inherent irritability of myocardial cells. Because of this suggestion, Haller became known as the father of the myogenic theory. Thirty-five years later (1794), Scarpa [8] found ganglia at the base of the heart in man, calf, and horse. In 1838, Remak [9] found ganglia and nerves in the coronary sulcus of man. By 1880 many Russian and French observers had found ganglia in the heart.

The discovery of nerve cells in the heart led Bichat,[6] as early as 1822, to state that the heart ganglia act as independent centers, that they may be considered as completely independent of the central nervous system, and that they are an ensemble of many little nervous systems. During the middle of the last century Volkmann [6] stated:

> The central organ of the heart-beat I assume to be the ganglia found by Remak. . . .
>
> . . . The ganglia as well as their intercommunicating nerve-fibers constitute a unified system . . . which binds together the contraction of countless muscle bundles into a purposeful unity and sequence. . . .
>
> If the communicating fibers are cut, each ganglion operates by its own inherent energy.

By 1880 the myogenic theory was all but buried because of the demonstration of an intrinsic nervous system in the heart. At that time Gaskell,[10] the brilliant

6. Cited by Hoff, H. E.: Vagal Stimulation Before the Webers, Ann. M. Hist. **8**:138, 1936; History of Vagal Inhibition, Bull. Hist. Med. **8**:461, 1940.

7. Haller, A.: Anfangsgründe der Physiologie der menschlichen Körpers, Berlin, C. F. Voss, 1759-1776 (8 volumes).

8. Cited by Perman, E.: Anatomische Untersuchungen über die Herznerven bei den höheren Säugetieren und beim Menschen, Ztchr. ges. Anat. (Abt. 1) **71**:382, 1924.

9. Remak, R.: Über die Ganglien der Herznerven des Menschen und deren physiologische Bedeutung, Wchnschr. ges. Heilk., 1839, p. 149.

10. Gaskell, W. H.: The Croonian Lecture: On the Rhythm of the Heart of the Frog, and on the Nature of the Action of the Vagus Nerve, Phil. Tr. London (1882) **173**:993, 1883.

English physiologist, had finished his work on the extrinsic nerves of the heart and had undertaken an investigation of its intrinsic nerves. He concluded that in the frog impulse formation and conduction are of neurogenic nature; but that in the tortoise impulse formation and conduction are of myogenic nature because the rhythmic beating continued after he had made zigzag cuts, which he believed had severed all nerve connections between the atria and the ventricle, and because he found indistinctly striated muscle fibers connecting atrium with ventricle. His conclusions resurrected the myogenic theory. However, Gaskell failed to establish that he had severed all nerve connections between atria and ventricle, and that the muscle fibers described were more embryonic than the working muscle cells and possessed special impulse-forming and impulse-conducting properties. Nevertheless, Gaskell shifted the attention from investigation of the intrinsic nervous system to a quest for anatomic proof to support the resurrected myogenic theory. The result was the finding of a sinoatrial node, an atrioventricular node, an atrioventricular bundle—the special muscle entities thought to function as impulse formers and conductors. These anatomic findings led to the development of an amazing number of theories to explain the observations. The net result of descriptions of the special conduction system of the heart, and the theories based upon them, is, in the words of Todd,[11] "one of the most garbled perversions of fact in modern science, salted with a pinch of truth to give it the tang of verity."

From the 1880's the intrinsic nervous system of the heart has received a stepchild's treatment from most anatomists, physiologists, and cardiologists, in spite of the fact that Carlson [12] in 1909 conclusively showed in the king crab that neither impulse formation and conduction nor rhythmic beating occurred after removal of the animal's intrinsic cardiac nerves.

While most of the investigators of cardiac impulse formation and conduction have been off on a "His-bundle detour," a considerable number of investigators have been studying the nerves of the hearts.[13] Progress has been slow. Knowledge

11. Todd, T. W.: Specialized Systems of the Heart, in Special Cytology, edited by Cowdry, E. V., Ed. 2, New York, Paul B. Hoeber, Inc., 1928, Vol. 2, p. 853.

12. Carlson, A. J.: Vergleichende Physiologie der Herznerven und der Herzganglien bei den Wirbellosen, Ergebn. Physiol. **8**:371, 1909.

13. (*a*) Vignal, W., cited by Michailow, S.: Innervation des Herzens im Lichte des neuesten Forschungen, Ztschr. wissensch. Zool. **99**:539, 1911-1912. (*b*) Eisenlohr, L.[8] (*c*) Ott, A.[8] (*d*) Weinreich, M.[8] (*e*) His.[4] (*f*) Dogiel, A. S.: Zur Frage über den feineren Bau der Herzganglien des Menschen und der Säugethiere, Arch. mikr. Anat. **53**:237, 1898. (*g*) Smirnoff, A. E.: Zur Frage von der Endigung der motorischen Nerven in den Herzmuskeln der Wirbeltiere, Anat. Anz. **18**:105, 1900. (*h*) Michailow, S.: Innervation des Herzens im Lichte des neuesten Forschungen, Ztschr. wissensch. Zool. **99**:539, 1911-1912. (*i*) Perman, E.: Anatomische Untersuchungen über die Herznerven bei den höheren Säugetieren und beim Menschen, Ztschr. ges. Anat. (Abt. 1) **71**:382, 1924. (*j*) Fakutake, K.: Beiträge zur Histologie und Entwichlungsgeschichte des Herznervenssystems, ibid. (Abt. 1) **76**:592, 1925. (*k*) Woollard, H. H.: The Innervation of the Heart, J. Anat. **60**:345, 1926. (*l*) Jones, T.: Intramuscular Nerve Elements of Ventricular Muscle, ibid. **61**:247, 1927. (*m*) Tsunoda, T., and Kasahara, I.: Vergleichendanatomische Studien über die Nervenendigungen des Herzmuskels, sowie über die Nervenversorgung des spezifischen Herzmuskelgewebes, Ztschr. Zellforsch. u. mikr. Anat. **7**:177, 1928. (*n*) Francillon, M. R.: Zur Topographie der Ganglien des menschlichen Herzens, Ztschr. ges. Anat. (Abt. 1) **85**:131, 1928. (*o*) Okamura, C.: Über die Ganglienzellen in der Herzwand, ibid. (Abt. 1) **89**:344, 1929. (*p*) Lasowsky, J. M.: Normale und pathologische Histologie der Herzganglien des Menschen, Arch. path. Anat. **279**:464, 1930. (*q*) King, A. B.: Nerve Endings

is still incomplete because of the large number of roadblocks encountered by the investigators. Although the greatest of these is probably professional apathy and indifference to the morphology and physiology of the cardiac nerves, there are others:

1. The intrinsic nervous system is diffusely distributed, and the location of its elements is not identical in any two hearts.

2. The relation between the extrinsic nerves and the intrinsic nerves is not clear: Some investigators hold that all the fibers from the sympathetic and parasympathetic systems which enter the heart terminate in and around intrinsic nerve cells; others, that all fibers from afar terminate on myocardial cells, blood vessel walls, fatty tissue, and connective tissue. Methods are not available by which fibers from intrinsic and extrinsic nerve cells can be distinguished as they lie together within nerves. Nonidez [13r] claims to be able to distinguish sympathetic from parasympathetic fibers with his recently developed stain. Brouha, Cannon, and Dill [14] and Michailow [13h] were able to destroy all extrinsic nerves to the heart and maintain the animal alive long enough to produce degeneration of the peripheral ends of the cut nerves. We have found their work difficult to repeat. However, with greater surgical skill and better postoperative management, it should be possible to keep animals alive long enough to allow all extrinsic fibers to degenerate, permitting the discernment of the architecture of the intrinsic nervous system.

3. Difficulty has been encountered in visualizing nerve endings: Older observers admitted that they were not able to see nerve endings in cardiac muscle. Among recent observers, some show beautiful drawings of nerve endings lying on the sarcoplasm of muscle fibers of the so-called conduction system and other myocardial cells; others show delicate nerve nets within the muscle cells. It, therefore, appears that investigators of cardiac nerves are well on the way to removing the formidable roadblocks.

PERSONAL OBSERVATIONS

Our observations on the topography of the cardiac nerve cells agree with those of others. It appears that the longer and more meticulous the search, the more nerve cells are found in the atria and in the atrioventricular groove. A few observers have noted nerve cells in the ventricles. The Glomsets found nerve cells in and around the branches of the ungulate bundle. Smirnoff [13s] found nerve cells scattered over the ventricles. One of us (K. R. C.) found a nerve cell in the upper part of the septum in man. (All observers agree that nerve cells are scarce in the lower chambers.) In the atria and in the atrioventricular groove ganglion cells are abundant, occurring underneath the visceral pericardium of the atria, occasionally within the myocardium, and in the loose connective tissue throughout the entire atrioventricular groove. The cells occur singly and in small or large groups. Single cells are found over both atria, about the mouths of the pulmonary veins, and in

in the Cardiac Muscle of the Rat, Bull. Johns Hopkins Hosp. **65**:489, 1939. (*r*) Nonidez, J. F.: Studies on the Innervation of the Heart: I. Distribution of the Cardiac Nerves, Am. J. Anat. **65**:361, 1939. (*s*) Glomset and Birge.[8] (*t*) Lavrentiev, B. I.: The Innervation of the Heart, Am. Rev. Soviet Med. **3**:229, 1946. (*u*) Hirsch, E. F., and Orme, J. F.: Sensory Nerves of the Human Heart, Arch. Path. **44**:325 (Oct.) 1947.

14. Brouha, L.; Cannon, W. B., and Dill, D. B.: The Heart Rate of the Sympathectomized Dog in Rest and Exercise, J. Physiol. **87**:345, 1936.

the atrioventricular groove. Single ganglia are also scattered over the atria and in the atrioventricular groove; smaller ones frequently lie in or near the nerve trunks. Small and large ganglia occur in chains in the following localities: around the mouths of the big veins, around the coronary sulcus, around the beginning of the aorta and the pulmonary arteries in the interatrial groove anteriorly and posteriorly

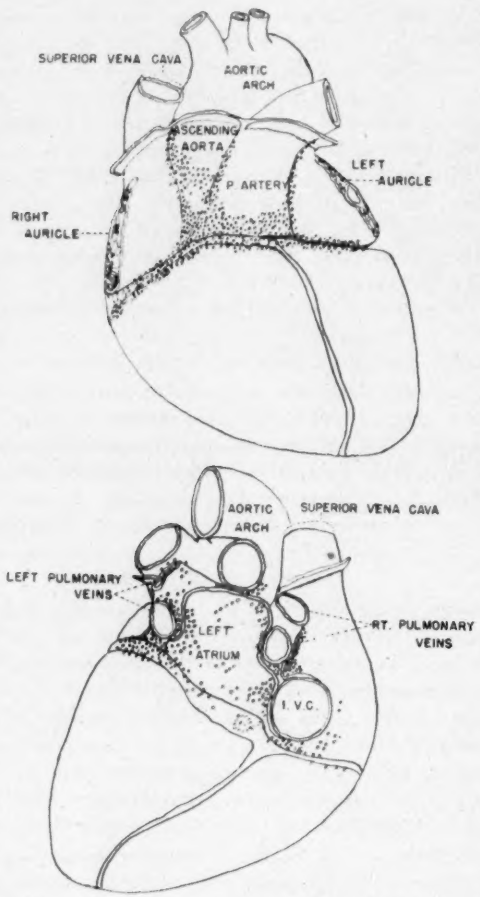

Fig. 2.—Schematic drawings of chains of ganglia in heart of man. *I. V. C.* indicates inferior vena cava.

(Fig. 2), and in the atrioventricular groove. The number of cells found in each ganglion varies from a few to hundreds. Dogiel [13f] described three types of intrinsic cardiac nerve cells, and Michailow,[13h] four types.

Nerve trunks, large and small, lie in abundance underneath the pericardium of atria and ventricles. These are readily visualized by a number of gross techniques

and also by histologic methods (Fig. 3). The trunks form a network around the entire myocardium, the larger ones usually being found near the coronary vessels. Their course is not dependent upon that of the blood vessel. Nerve trunks sometimes penetrate the ventricular myocardium far away from the blood vessels. The

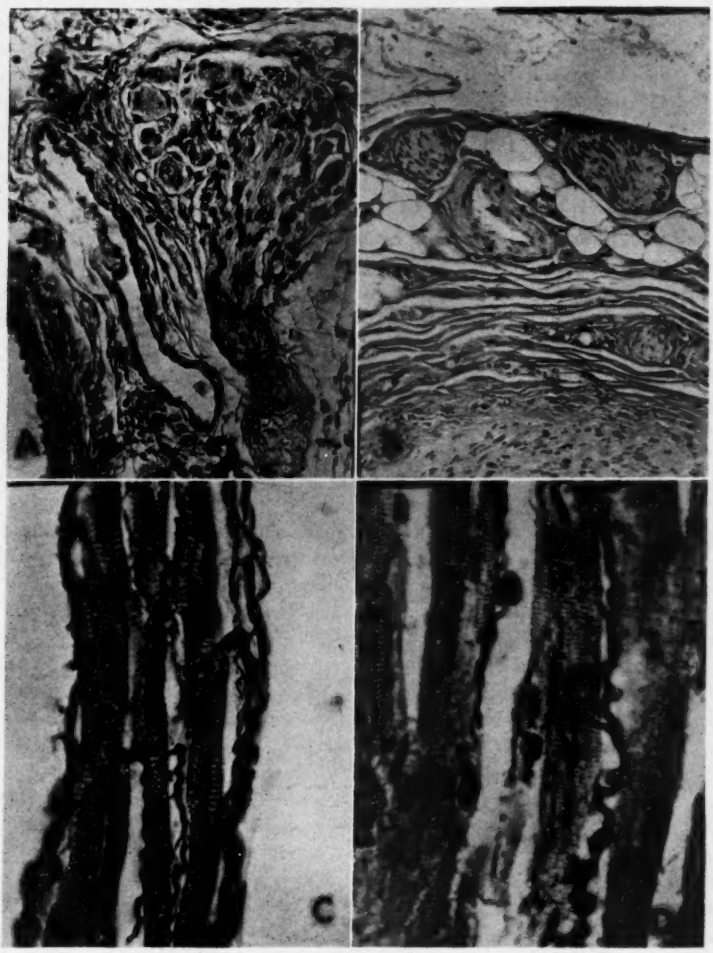

Fig. 3.—Photomicrographs of nerves in heart of man. *A*, ganglion in auriculoventricular groove. *B*, nerve trunks in pericardium near a coronary artery. Hematoxylin and eosin stain; × 180. *C*, intercellular plexus of nerve fibrils in ventricular myocardium with nerve endings. *D*, nerve ending on a muscle cell. Bodian stain; × 550.

smaller trunks occur farther away from neighboring vessels and near the apex. In the atria and in the atrioventricular groove there are often seen ganglia sending their entire output of fibers into a neighboring nerve trunk. Smaller collections

of nerve fibers leave the larger trunks, forming plexuses in pericardium and endocardium and within the blood vessel wall, as well as within the myocardium.

We have been especially interested in the plexuses within the myocardium. All the muscle bands of the atria and the ventricles are, as it were, wrapped up in a network of slender nerve trunks from which delicate plexuses are formed around individual muscle fasciculi and more delicate ones around individual muscle cells (Fig. 3). Throughout the myocardium we have frequently found delicate, tortuous, varicose, nerve fibrils lying on the individual cells. In good preparations, stained by Bodian's method,[15] we observed with amazement the abundance of nerve fibers within the myocardium and are inclined to agree with Smirnoff,[13f] who thought that every muscle fiber within the heart is supplied with motor nerve endings.

CONCLUSION

Until it is proved that the nerve cells within the heart do not originate the cardiac impulse and that the impulse is not carried by the fibers of these cells to the individual units of the myocardium, it is folly and waste of mental energy to develop theory upon theory to explain impulse formation and conduction on the basis of a nonexistent muscular conduction system.

15. Dr. W. R. Ingram, Professor and Head of the Department of Anatomy, State University of Iowa College of Medicine, Iowa City, had the Bodian stain applied to our sections of the myocardium that show the intramuscle fasciculi nerve plexuses, as well as the nerve endings on the myocardial fibers.

EDEMA AND HYPONATREMIA

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EDEMA and hyponatremia represent deviations of two characteristics of the internal environment that are usually maintained within narrow limits. These abnormalities involve alterations in physiologic equilibria which may be better understood if their analysis is prefaced by a consideration of the normal regulatory processes involved in the metabolism of salt and water.

The ultimate responsibility for the maintenance of a normal volume and tonicity of the body fluids devolves on the kidneys. The modern concept of renal physiology envisages the transformation of a large volume of glomerular filtrate to a much smaller volume of bladder urine which has been altered with respect to composition, concentration, and pH. The renal tubular epithelium is responsible for these alterations. The proximal portion of the tubule is largely responsible for the decrease in volume of the filtrate and, to less extent, for alterations in composition. However, it is in the distal tubule that the urine is made more or less concentrated than the parent filtrate, where salt and water may be differentially treated, and where potassium, hydrogen, and ammonia may be added. This discussion will concern itself in particular with those factors that may modify the activity of the cells of the distal tubule with respect to the reabsorption of salt and water. Although the volume and composition of the glomerular filtrate may play some role in determining the magnitude of the rates of excretion of salt and water, variations in the rates of tubular reabsorption of these materials appear to be more important considerations.

Verney [1] demonstrated that the injection of a small volume of hypertonic salt solution into the internal carotid artery of a dog undergoing a water diuresis promoted an antidiuretic response. An antidiuresis was also promoted by the intracarotid injection of hypertonic solutions of sucrose and dextrose, but not urea. Salt, sucrose, and dextrose are distinguished from urea in that they are unable to penetrate the cell membrane by the simple process of diffusion. Therefore, they exert an effective osmotic pressure at the cell membrane, which is not true of urea. Verney postulated the existence of osmoreceptors somewhere in the branches or distribution of the internal carotid artery which respond to variations in the effective osmotic pressure of the fluid in their milieu. An increase in the tonicity of the fluid stimulates this receptor, which transmits the stimulus through the supraopticohypophyseal pathway, causing the secretion of the antidiuretic hormone of the posterior pituitary

From the Department of Internal Medicine, Yale University School of Medicine.

Read before the Fall Clinical Session of the Maine Medical Association, Lewiston, Maine, Oct. 29, 1951.

1. Verney, E. B.: Croonian Lecture: The Antidiuretic Hormone and the Factors Which Determine Its Release, Proc. Roy. Soc., London, s. B **135**:25, 1947.

gland. Similarly, a decrease in the tonicity of the fluid bathing this receptor leads to a reduced stimulus to the posterior pituitary and a graded suppression of secretion of antidiuretic hormone. This hormone acts on the cells of the distal tubules to promote an increased rate of reabsorption of water.

A considerable body of evidence has been presented which strongly suggests that the posterior pituitary gland may respond to a stimulus other than tonicity. Martin, Herrlich, and Fazekas [2] reported the presence of increased antidiuretic activity in the urine of normal cats after they had been depleted of salt and rendered hyponatremic. More recently, Leaf and Mamby [3] observed increased antidiuretic activity in the sera of dogs with contracted extracellular volume and hyponatremia. Holmes and Cizek [4] demonstrated an increase in thirst with some retention of water in excess of salt in dogs whose extracellular fluid and plasma volumes had diminished as a result of salt depletion. Brun, Knudsen, and Raaschou [5] studied the change in the rate of excretion of water promoted by the assumption of the passive erect posture in normal subjects. They found a distinct antidiuresis which was sustained for some time after the subjects had reverted to the supine position. In similar circumstances subjects with diabetes insipidus responded with a much less intense and quite transient antidiuresis. These same observations were reported by Judson and his co-workers,[6] who employed the technique of experimental venous congestion of the limbs to induce the antidiuretic response. Brun and associates [7] also demonstrated that blood donated by a normal subject after a period in the passive erect posture promoted an antidiuretic response in a normal subject in circumstances of a water diuresis. This did not obtain if the blood was donated by a subject with diabetes insipidus after a similar period in the passive erect posture. These data suggest that another stimulus serving to promote an increase in secretion of antidiuretic hormone by the posterior pituitary gland is a decrease in the plasma volume or some function of such a decrease.

Other workers have presented data which represent the reciprocal of the above. Welt and Orloff [8] reported a marked increase in the rate of excretion of water induced by expansion of the plasma volume with an infusion of iso-oncotic albumin. Figure 1 describes the alterations in rate of excretion of water induced by infusions of 4, 5, and 6% solutions of albumin in isotonic sodium chloride solution compared

2. Martin, S. J.; Herrlich, H. C., and Fazekas, J. F.: Relation Between Electrolyte Imbalance and Excretion of an Antidiuretic Substance in Adrenalectomized Cats, Am. J. Physiol. **127**:51, 1939.

3. Leaf, A., and Mamby, A. R.: An Antidiuretic Mechanism Not Regulated by Extracellular Fluid Tonicity, abstracted, J. Clin. Invest. **30**:654, 1951.

4. Holmes, J. H., and Cizek, L. J.: Observations on Sodium Chloride Depletion in the Dog, Am. J. Physiol. **164**:407, 1951.

5. Brun, C.; Knudsen, E. O. E., and Raaschou, F.: The Influence of Posture on the Kidney Function, Acta med. scandinav. **122**:315 and 332, 1945.

6. Judson, W. R.; Epstein, F. H.; Tinsley, C. M.; Burrows, B. A., and Wilkins, R. W.: The Hemodynamic and Renal Functional Effects of Venous Congestion of the Limbs in Patients with Diabetes Insipidus, abstracted, J. Clin. Invest. **29**:826, 1950.

7. Brun, C.; Hilden, T., and Raaschou, F.: Kidney Function and Circulatory Collapse: Post-Syncopal Oliguria, J. Clin. Invest. **25**:568, 1946.

8. Welt, L. G., and Orloff, J.: The Effects of an Increase in Plasma Volume on the Metabolism and Excretion of Water and Electrolytes by Normal Subjects, J. Clin. Invest. **30**:751, 1951.

with the effect of an infusion of an equal volume of isotonic sodium chloride solution. It is readily seen that in each instance the infusion of albumin, in these concentrations, promoted an increase in the rate of excretion of water far in excess of that associated with the infusion of plain isotonic sodium chloride solution. Similar phenomena are observed when the vehicle for the albumin is 5% dextrose in water. They suggested that an increase in plasma volume suppressed the secretion of the antidiuretic hormone. Strauss and associates [9] have supplied evidence in support of this contention. These workers were unable to increase the rate of excretion of water with this type of infusion after the posterior pituitary gland had been already suppressed by hypotonicity of the body fluids induced with a large water load.

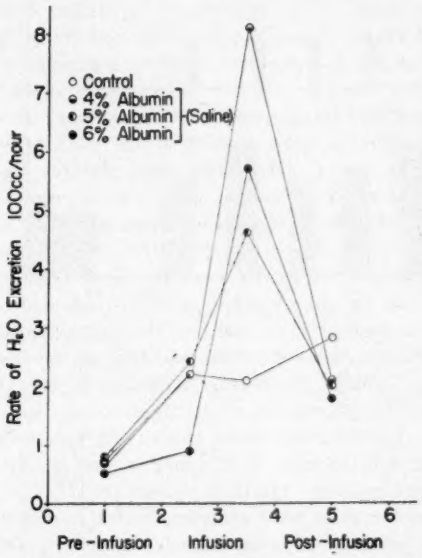

Fig. 1.—Effect of increase in plasma volume on rate of excretion of water.

It appears that the most important consideration concerning the rate of excretion of water is the extent to which it is reabsorbed in the distal tubule. The distal tubular reabsorption of water is under the influence of the secretion of the posterior pituitary gland, and this, in turn, may be modified by alterations in tonicity and, to less extent, volume.

The rate of excretion of salt is, similarly, a reflection of the degree to which it is reabsorbed by the renal tubule. It may well be that certain aspects of tubular reabsorption of salt (in the proximal tubule) are conditioned by the rate of filtration of sodium and chloride. However, variations in tubular activity, especially in the distal tubule, appear to be more important.

9. Strauss, M. B.; Davis, R. K.; Rosenbaum, J. D., and Rossmeisl, E. C.: The Production of Increased Renal Sodium Excretion by the Hypotonic Expansion of Extracellular Fluid Volume in Recumbent Subjects, to be published.

The concentration of sodium in the serum plays a role in determining its rate of excretion in the urine.[10] However, the various factors that may condition a particular concentration of sodium in serum appear to have an even greater influence in modifying its rate of excretion. If the concentration of sodium in the serum is increased in a normally hydrated subject by the administration of salt in excess of water, sodium will be excreted more rapidly than if the same serum concentration is attained by virtue of a loss from the body of water in excess of salt. The rate of excretion of sodium following administration of a certain amount of salt to a subject who has had no access to sodium chloride for a prolonged period will be slower than if the same amount of salt is given to a subject who has had free access to dietary salt. The concentration of sodium in the serum in each subject may, nevertheless, be the same. The infusion of hypertonic dextrose or mannitol solution in a normal subject promotes a markedly accelerated rate of excretion of salt.[11] Since mannitol and, to less extent, dextrose are unable to penetrate the cell membranes freely, they exert an effective osmotic force which moves water from the cells to the extracellular compartment. This movement of water depresses the concentration of sodium in the serum; yet it is at this time that the rate of excretion of salt increases. The sitting and passive erect postures[12] reduce the rate of excretion of salt. The effect of posture appears to be mediated via the adrenal cortex, since the antisaluresis in the passive erect posture is not marked and is transient in the subject with adrenal insufficiency.[13] Figure 2 presents the results of a study of the effects of the passive erect posture in a patient with Addison's disease. The period in the passive erect posture is indicated by the word "tilt." This patient was at an angle of 35 degrees, and the posture lasted 30 minutes. The decrease in the rate of excretion of sodium was less intense than the reduction in the rate of excretion of water. Moreover, the antidiuretic response was still clearly evident in the last period, whereas the excretion of sodium had already returned to the recumbent rate. The difference in the intensity of response is even more striking when the values for the ratio E/F (amount excreted/amount filtered) for sodium and water are compared. Harrison and his group[14] have demonstrated that some intracranial function must be of great importance in modifying salt excretion. They found that an inflated cuff about the neck obviated the decrease in rate of excretion of salt in the sitting posture.

10. Welt, L. G.; Goodyer, A. V. N.; Darragh, J., and Abele, W.: The Role of Tonicity of the Body Fluids in Determining the Rate of Excretion of Sodium, unpublished observations.

11. Seldin, D. W., and Tarail, R.: Effect of Hypertonic Solutions on Metabolism and Excretion of Electrolytes, Am. J. Physiol. **159**:160, 1949.

12. Epstein, F. H.; Goodyer, A. V. N.; Lawrason, F. D., and Relman, A. S.: Studies of the Antidiuresis of Quiet Standing: The Importance of Changes in Plasma Volume and Glomerular Filtration Rate, J. Clin. Invest. **30**:63, 1951. Strauss, M. B.; Davis, R. K.; Rosenbaum, J. D., and Rossmeisl, E. C.: "Water Diuresis" Produced During Recumbency by the Intravenous Infusion of Isotonic Saline Solution, ibid. **30**:862, 1951.

13. Welt, L. G.: The Effects of the Passive Erect Posture on the Rates of Excretion of Salt and Water in the Adrenal-Insufficient Subject, unpublished observations.

14. Lewis, J. M., Jr.; Buie, R. M.; Sevier, S. M., and Harrison, T. R.: The Effect of Posture and of Congestion of the Head on Sodium Excretion in Normal Subjects, Circulation **2**:822, 1950. Viar, W. N.; Oliver, B. B.; Eisenberg, S.; Lombardo, T. A.; Willis, K., and Harrison, T. R.: The Effect of Posture and of Compression of the Neck on Excretion of Electrolytes and Glomerular Filtration: Further Studies, ibid. **3**:105, 1951.

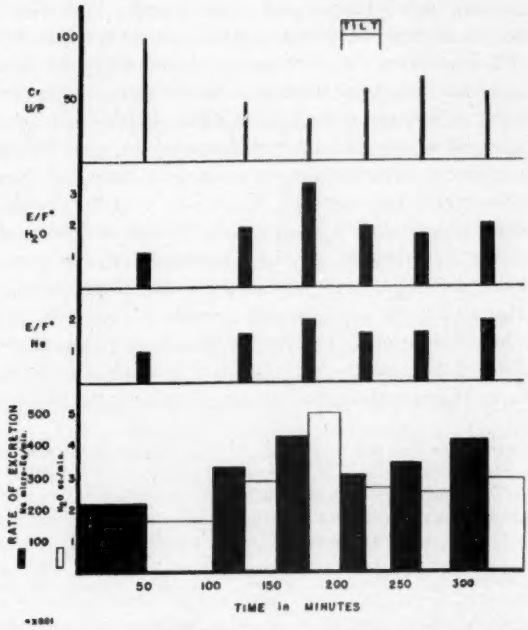

Fig. 2.—Responses of patient (D. W., B 37944) with Addison's disease to assumption of passive erect posture (tilt). *Cr U/P* indicates urinary/plasma ratio of creatinine. *E/F H_2O* means water excreted/water filtered; *E/F Na* means sodium excreted/sodium filtered.

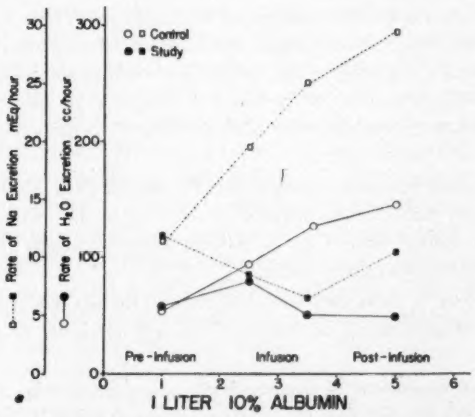

Fig. 3.—Effect of increase in colloid osmotic (oncotic) pressure on rates of excretion of sodium and water.

Goodyer, Peterson, and Relman [15] and, more recently, Welt and Orloff [8] have demonstrated that an increase in plasma volume induced by infusions of hyperoncotic (25 or 10%) solutions of salt-poor human albumin promotes a decrease in the rate of excretion of salt in normal subjects. Figure 3 presents the changes in the rates of excretion of sodium and water induced by an infusion of 1 liter of a solution of 10% albumin in saline solution and an infusion of the same volume of isotonic sodium chloride solution. The rates of excretion were almost identical in the two studies during the preinfusion period. There was a sharp rise in the rate of excretion of sodium associated with the infusion of isotonic sodium chloride solution. However, when the hyperoncotic solution of albumin was infused, the rate of excretion of sodium declined. Since an increase in the plasma volume per se does not have this effect, it may be related to the decrease in interstitial fluid volume or the increase in the colloid osmotic pressure of the plasma. It has been suggested [8] that the increase in colloid osmotic pressure may stimulate an oncoreceptor which may promote the increased reabsorption of salt. Whatever the mechanism, it is not

Influence of Increase or Decrease in Tonicity of Body Fluids, of Increase or Decrease in Plasma Volume, and of Increase in Plasma Oncotic Pressure on Rates of Excretion of Salt and Water

	Tonicity		Volume		Oncotic Pressure	
Rate of Excretion	I Increase	II Decrease	III Increase	IV Decrease	V Increase	VI Decrease
A. Water	−	+	+	−	?	?
B. Salt	+	−	+	−	−	?

mediated via the adrenal cortex, since the same observations were obtained in a subject with adrenal insufficiency.

All this evidence suggests that one of the factors that influences the rate of excretion of salt is plasma volume or one of its functions. These data further suggest that among the functions of plasma volume must be considered the concentration of serum proteins, the volume and the pressure within some key portion of the vascular system, the disposition of the blood as this may be influenced by posture and other hemodynamic considerations, and, perhaps, the viscosity and rate of flow of blood.

The table presents in summary form the influence of an increase or decrease in tonicity of the body fluids, of an increase or decrease in the volume of the plasma or some function thereof, and of an increase in oncotic pressure of the plasma on the rates of excretion of salt and water.

This schema may be examined with reference to the various types of expansion and contraction of body fluids as they may be seen clinically or induced experimentally.

1. An isotonic expansion of volume will induce alterations IIIA and IIIB, thus promoting an increased rate of excretion of water and salt.

15. Goodyer, A. V. N.; Peterson, E. R., and Relman, A. S.: Some Effects of Albumin Infusions on Renal Function and Electrolyte Excretion in Normal Man, J. Appl. Physiol. **1**:671, 1949.

2. A hypotonic expansion of volume (e. g., a water load) will induce alterations IIA, IIB, IIIA, and IIIB. Since IIB and IIIB are opposite in direction, the net effect on salt will be determined by which of these alterations is larger. The main effect, however, will be an increased rate of excretion of water.

3. A hypertonic expansion of volume induces alterations IA, IB, IIIA, and IIIB. Since IA and IIIA are opposite, the net effect on water will be determined, in part, by the relative strength of these stimuli. The major effect is an increased rate of excretion of salt.

4. An isotonic contraction of volume induces alterations IVA, IVB, and VB. These promote a decreased rate of excretion of salt and water.

5. A hypotonic contraction of volume induces alterations IIA, IIB, IVA, IVB, and VB. IIA and IVA will tend to neutralize each other, and the major effect is a decrease in the rate of excretion of salt.

6. A hypertonic contraction of volume induces alterations IA, IB, IVA, IVB, and VB. IB and IVB tend to neutralize each other, and the net effect is a decreased rate of excretion of water and salt. Although this schema is admittedly incomplete, it appears to be grossly compatible with the known facts.

Edema, which is an increase in the volume of the extravascular component of the extracellular compartment, results from an alteration in the Starling equilibrium which promotes an increased rate of transudation of fluid from the plasma to the interstitial fluid.[16] In congestive heart failure it is the generalized increase in venous pressure; in cirrhosis with ascites it is an increase in pressure in the portal system (perhaps with an inability to remove protein from the peritoneal cavity), and in the nephrotic syndrome it is a decrease in the colloid osmotic pressure of the plasma. With this definition of edema in mind, it is clear that at the time edema is forming transudation of fluid from the plasma must proceed at a faster rate than it is reabsorbed into the blood stream. Thus, regardless of the actual magnitude of the volume of the plasma, the dynamics of the equilibrium between the vascular and extravascular compartments are such as to present the physiologic stimulus of a diminishing plasma volume. This stimulus of a decreasing plasma volume promotes the retention of salt and water. If these materials are made available, they are retained in slightly hypotonic proportions. The disposition of this increment in volume of the extracellular compartment between the plasma and the interstitial fluid depends on the severity of the dislocation in the Starling equilibrium. The severer the dislocation, the more of the retained saline solution will gain access to the interstitial fluid, and the less will the volume of the plasma be restored. This permits the stimulus from the diminished plasma volume to persist, and the retention of salt and water continues; so long as a disproportionate volume of retained fluid passes into the extravascular compartment, the volume of the plasma will appear to be diminishing.

16. Peters, J. P.: The Role of Sodium in the Production of Edema, New England J. Med. **239**:353, 1948; Sodium, Water and Edema, J. Mt. Sinai Hosp. **17**:159, 1950; The Problem of Cardiac Edema, Am. J. Med., to be published. Welt, L. G., and Seldin, D. W.: The Pathologic Physiology and Treatment of Edema, Technical Bulletin 10-69, Veterans Administration, Jan. 12, 1951.

On the other hand, if the dislocation is minor or self-limited as in phlebitic edema, the retention of salt and water will restore the plasma volume. This, in turn, mitigates the intensity of the stimulus contributed by the decreasing plasma volume, and a new equilibrium with an expanded interstitial fluid volume is achieved.

If the dietary salt is not available, the decreasing plasma volume cannot be fully compensated. This more intense stimulus may now be sufficient to promote the secretion of antidiuretic hormone, and there is an increased tubular reabsorption of water. This retention of water without salt dilutes the body fluids, causing hyponatremia. Thus, the general tendency toward mild hyponatremia among patients with edema is exaggerated if dietary salt is drastically restricted. The degree to which this chronic dilution hyponatremia may proceed is dependent on the strength of the stimulus derived from the contracting plasma volume and is ultimately limited by the hypotonicity itself. The latter suppresses the secretion of the antidiuretic hormone, and eventually this suppressive influence of hypotonicity matches the stimulating effect of the contracted volume.

The majority of patients with edema and chronic dilution hyponatremia do not present the signs and symptoms that characterize hyponatremia in the absence of edema. It may well be that this slow development of dilution hyponatremia allows time for some physiologic readjustment to develop. Nevertheless, chronic dilution hyponatremia represents a grave clinical state and usually denotes a very poor prognosis. Correction of the reduced concentration of sodium in the serum to normal levels in these patients promotes thirst, increased ingestion and retention of water, with redilution, and no essential change in the clinical status except increased edema.

In some patients with edema a chronic dilution hyponatremia may develop in a manner unrelated specifically to the alterations in the Starling equilibrium. There is suggestive evidence that certain patients with long-standing, chronic, severely debilitating illnesses associated with malnutrition and wasting may display a metabolic defect characterized by a primary decrease in cellular osmolarity.[17] The immediate response to such a change would be a movement of water from the cells to the extracellular fluid in the interests of osmotic equilibrium. This increment of water in the extracellular compartment would, in itself, depress the concentration of sodium in this compartment. In order to reestablish the original distribution of water between these two components of body fluid, salt must be excreted or water retained. The only alternative for a patient who is unable to excrete salt is the retention of water. These patients resemble the first group in that they would not present any disability arising from the hyponatremia per se. In fact, the depressed concentration of sodium in the serum must be considered "normal" for them. As in the first instance, its most relevant feature would be the fact that it represents a grave prognostic sign.

There is, on the other hand, a third group of patients with edema and hyponatremia who present a somewhat different problem. These are the patients who have sustained an acute loss of salt and water either by accident or intent and who,

17. Welt, L. G.; Orloff, J.; Kydd, D. M., and Oltman, J. E.: An Example of Cellular Hyperosmolarity, J. Clin. Invest. **29**:935, 1950. Sims, E. A. H.; Welt, L. G.; Orloff, J., and Needham, J. W.: Asymptomatic Hyponatremia in Pulmonary Tuberculosis, ibid. **29**:1545, 1950.

presumably in response to this loss of volume, have an antidiuretic response with the retention of water and the consequent development of an acute hyponatremia. This is a combination of water intoxication and peripheral vascular collapse. The clinical manifestations are anorexia, lassitude, clouding of consciousness, coma, renal decompensation with oliguria, and nitrogen retention. These symptoms and signs may be distinctly, and sometimes dramatically, improved with correction of the depressed concentration of sodium in the serum. A diuresis with the delivery of some edema fluid has been observed in such patients after restoration of the tonicity of the extracellular water to normal. It should be mentioned that correction of the tonicity is followed by expansion of the volume of the extracellular fluid, and it is probable that the clinical improvement is associated with the change in volume, as well as in tonicity. This point has not been specifically examined.

This syndrome may develop as the result of acute large losses of fluid and electrolytes associated with vomiting and diarrhea from a variety of causes. However, it probably develops more commonly after overenthusiastic use of mercurial diuretics in persons with cardiac disease and the sudden delivery of very large ascitic collections in cirrhotic patients by paracentesis. The latter situation has been studied by several groups of investigators.[18] These studies reveal that after a large paracentesis the hematocrit and hemolgobin levels rise, indicating a contraction of plasma volume. This presumably occurs as the result of an increase in the rate of transudation of fluid into the ascitic sac as a consequence of the sharp decrease in intraperitoneal pressure that had been a force opposing transudation. These patients may complain of thirst and, if they are allowed free access to water, ingest and retain enough to cause a dilution of the electrolytes of the body fluids. It is at this time that symptoms referable to the state of consciousness may appear, along with hypotension and evidences of renal decompensation. There is evidence that this syndrome may be prevented by supporting volume with salt and water or by an infusion of human serum albumin. It would probably not occur if the removal of a tremendous ascitic collection were done in several stages separated by a day or two. Figure 4 presents the sequence of events in a patient with cirrhosis following the removal of a large ascitic collection by paracentesis. Thirteen and five-tenths liters was removed in a 30-minute period at 9 p. m., March 29. No food or liquid was allowed until the next morning. At this time there was a significant increase in hematocrit from 32.5 to 37.0 vol. %. Free access to water allowed the ingestion and retention of a sufficient volume to dilute the concentration of sodium in the serum from 124.5 to 116.5 mEq. per liter by April 4. The patient had become lethargic, poorly responsive, and disoriented. The nonprotein nitrogen of the blood rose from 51 to 69 mg. per 100 cc. The elevated hematocrit at this time is a reflection of red cell swelling with water secondary to hypotonicity of its fluid environment. After the infusion of 1 liter of 3% salt solution on April 4 and 5, the concentration of sodium in the serum rose to 132 mEq. per liter, the nonprotein nitrogen decreased to 53 mg. per 100 cc., and the sensorium returned to normal.[18a]

18. (*a*) Seldin, D. W., and Welt, L. G.: The Mechanism of Acute Dilution Hyponatremia in Patients with Cirrhosis and Ascites, to be published. (*b*) Nelson, W. P., III; Rosenbaum, J. D., and Strauss, M. B.: Manifestations of Sodium Deficit in Hepatic Cirrhosis with Ascites, J. Clin. Invest. **30**:738, 1951.

Each patient with edema and hyponatremia presents a particular problem that must be analyzed and evaluated in the light of the circumstances in which that patient may have acquired the hyponatremia. The most important data for this evaluation are derived from the history and clinical status of the patient. In particular, information should be sought concerning recent losses of fluid. The commonest of these have already been mentioned. Somnolence, clouding of consciousness, coma, falling blood pressure, and nitrogen retention all suggest an acute rather than a chronic dilution hyponatremia.

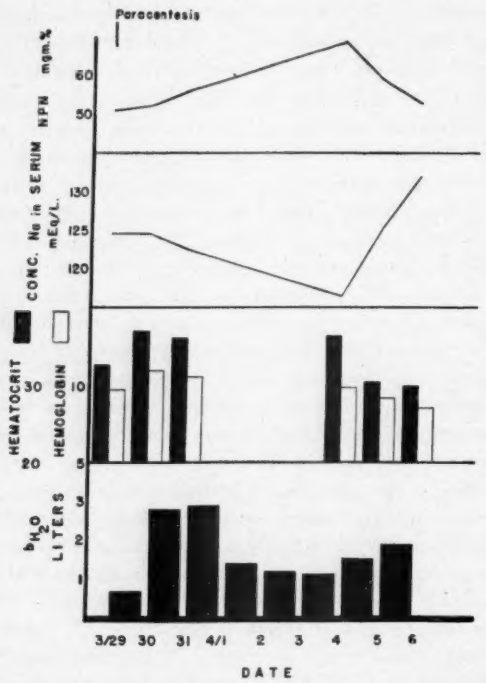

Fig. 4.—Antidiuretic response of patient (D. C., C 25661) following paracentesis of large collection of ascitic fluid. bH_2O means body water.

Once suspected, the diagnosis of hyponatremia can be established only by an analysis of the serum for the concentration of sodium. An estimate of the concentration of sodium from the concentration of chloride in the serum may be quite misleading. A decrease in the concentration of chloride in the serum may be a reflection of a respiratory acidosis or a metabolic alkalosis due to the loss of chloride in excess of sodium in response to a mercurial diuretic.[19] In either instance the concentration of sodium in the serum may be quite normal. An estimate of the concentration of sodium from the sum of the concentrations of bicarbonate and

19. Schwartz, W. B., and Wallace, W. M.: Electrolyte Equilibrium During Mercurial Diuresis, J. Clin. Invest. **30**:1089, 1951.

chloride in the serum is less hazardous [20] but may still be inaccurate. This is especially true when the nonprotein nitrogen of the blood is elevated and the concentration of undetermined fixed acids in the serum is increased.

If it is decided in any given instance to correct the hyponatremia in the patient with edema, this must be done with hypertonic saline solution. The concentration of sodium in the administered fluid must be greatly in excess of its concentration in the extracellular water, if the concentration of sodium in the latter is to be raised without producing a tremendous expansion of the extracellular compartment.

A uniform osmotic pressure throughout all the body fluids demands that an increase in the concentration of sodium in the extracellular water must be accompanied with the same increase in the concentration of milliosmoles in the cell water. This increase in intracellular concentration will be accomplished by the movement of water from the cells in response to the addition of hypertonic salt to the extracellular space. Since the increase in osmolar concentration throughout the entire body water will be caused by adding salt to the extracellular phase, it is as if the

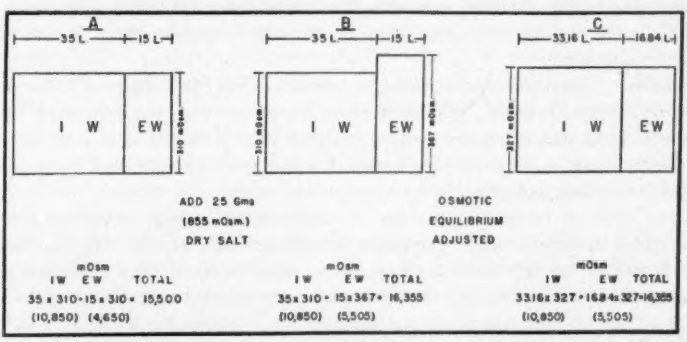

Fig. 5.—Redistribution of water between cellular and extracellular compartments induced by adding dry sodium chloride to extracellular fluid. *IW* indicates intracellular water; *EW*, extracellular water.

salt itself were being distributed throughout the entire body water. Although the administered salt will, in fact, be confined to the extracellular compartment, its osmotic effect is distributed throughout both compartments.[21]

This may be illustrated more clearly in Figure 5. In these representations of total body water, the length of the horizontal axis defines the volume of fluid, and the height defines the concentration of nondiffusible solutes, i. e., the milliosmolar concentration. In this particular instance, as noted in *A* of Figure 5, the volume of total body water is 50 liters; 35 liters is in the intracellular compartment, and 15 liters is in the extracellular compartment. The concentration of nondiffusible solutes, 310 milliosmoles per liter, is the same in each compartment. This is a consequence of the fact that the membrane separating these two compartments is permeable to water, which, therefore, must distribute itself so as to maintain osmotic

20. Hald, P. M.; Heinsen, A. J., and Peters, J. P.: The Estimation of Serum Sodium from Bicarbonate plus Chloride, J. Clin. Invest. **26**:983, 1947.

21. Peters, J. P.: The Treatment of Salt Depletion, Surgery **24**:568, 1948.

uniformity. The total number of milliosmoles is $35 \times 310 + 15 \times 310$, or 10,850 within the cells and 4,650 in the extracellular water, which equals 15,500. *B* represents the first but very transient change that is promoted by the addition of 25 gm. (855 milliosmoles) of dry salt to the extracellular fluid. This addition of salt increases the number of milliosmoles in the extracellular water to 5,505. If it is assumed that there is a moment before a redistribution of water occurs, the concentration in this compartment for that moment will be 367 milliosmoles per liter. Since water permeates the cell membrane freely, there will be a movement of water from the cells until the concentrations of milliosmoles in each compartment are again equal. This is depicted in *C* of Figure 5. It should be emphasized that there has been an increase in the milliosmolar concentration in the cells without any addition of solutes to that compartment, and, further, that the added salt has been diluted by water derived from the cells. This has been brought about as a direct consequence of the introduction of salt into the extracellular compartment in such a way as to raise the concentration of sodium and chloride in that compartment. Since an increase in the concentration of sodium salts can be achieved only with the same increase in the concentration of solutes within the cells, the amount of salt needed to raise its concentration must be calculated on the basis of the entire volume of body water.

Therefore, to correct hyponatremia, hypertonic (3 to 5%) saline solution should be administered in amounts calculated from the product of the estimated volume of the total body water and the desired increase in concentration of sodium. After correction of the hyponatremia, the intake of water must be restricted for a suitable period if immediate redilution is to be avoided.

In the light of present knowledge it might be tentatively suggested that the clinical status of patients with edema and acute hyponatremia may well be improved by correction of the depressed tonicity. Most patients with chronic dilution hyponatremia are not benefited by this procedure. In those instances in which it is difficult to classify the nature of the disorder, it is justifiable to make the therapeutic test.

Case Reports

CONGENITAL COARCTATION OF THE ABDOMINAL AORTA WITH RESULTANT RENAL HYPERTENSION

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AND
A. C. CORCORAN, M.D.
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ESTABLISHMENT of experimental hypertension by compression of one or both renal arteries with a metal clamp [1] directed attention to lesions of main renal arteries as causes of hypertension in man. Some investigators [2] believed that they could demonstrate at autopsy a high incidence of arteriosclerotic narrowing in fixed preparations of renal arteries from hypertensive patients. However, Lisa and associates [3] could not show a relation between the level of arterial pressure during life and the caliber of the renal arteries in fresh preparations. Yuille [4] reviewed the relation between lesions of main renal arteries and hypertensive disease and discounted the participation of renal arteriosclerosis in the genesis of this condition. He pointed out that the lesions of large vessels were commonly associated with intrarenal arteriolar sclerosis and that both were presumably results and not causes of hypertensive disease. Had the arterial lesions been primary, then, as in experimental renal hypertension in rats,[5] arteriolar lesions should not have developed distal to the point of arterial narrowing.

Thus, closer scrutiny showed that hypertensive disease is only infrequently attributable to lesions of major renal vessels. Such hypertension has occurred in cases of renal arterial embolization,[6] thrombosis,[7] syphilitic occlusion,[8] and aneu-

From the Department of Pathology and Research Division of the Cleveland Clinic Foundation and Frank E. Bunts Educational Institute.

1. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia: Harvey Lecture, Bull. New York Acad. Med. **14**:523-553 (Sept.) 1938.

2. Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of Main Renal Arteries in Association with "Essential" Hypertension in Man, Bull. Johns Hopkins Hosp. **65**:353-375 (Nov.) 1939. Richardson, G. O.: Atherosclerosis of Main Renal Arteries in Essential Hypertension, J. Path. & Bact. **55**:33-39 (Jan.) 1943

3. Lisa, J. R.; Eckstein, D., and Soloman, C.: Relationship Between Arteriosclerosis of Renal Artery and Hypertension: Analysis of 100 Necropsies, Am. J. M. Sc. **205**:701-703 (May) 1943.

4. Yuille, C. L.: Obstructive Lesions of Main Renal Artery in Relation to Hypertension, Am. J. M. Sc. **207**:394-404 (March) 1944.

5. Wilson, C., and Byron, F. B.: Vicious Circle in Chronic Bright's Disease: Experimental Evidence from the Hypertensive Rat, Quart. J. Med. **10**:65-93 (April) 1941.

6. Fishberg, A. M.: Hypertension Due to Renal Embolism, J. A. M. A. **119**:551-553 (June 13) 1942. Prinzmetal, M.; Hiatt, N., and Tragerman, L. J.: Hypertension in Patient with Bilateral Renal Infarction: Clinical Confirmation of Experiments in Animals, ibid. **118**:44-46 (Jan. 3) 1942.

7. Yuille.[4] Saphir, O., and Ballinger, J.: Hypertension (Goldblatt) and Unilateral Malignant Nephrosclerosis, Arch. Int. Med. **66**:541-560 (Sept.) 1940.

8. Price, R. K., and Skelton, R.: Hypertension Due to Syphilitic Occlusion of Main Renal Arteries, Brit. Heart J. **10**:29-33 (Jan.) 1948.

rysm.[9] A striking example is the patient described by Leadbetter and Burkland,[10] whose right renal artery was all but occluded by a mass of smooth muscle; removal of the right kidney relieved the concurrent severe hypertension.

The purpose of this report is to describe clinical and autopsy observations in an apparently unique case, in which the syndrome of malignant hypertension occurred as the result of bilateral stenosis of the orifices of the main renal arteries. These renal arterial lesions were sequential to focal coarctation of the abdominal aorta.

REPORT OF CASE

A boy, aged 14, was examined in the Cleveland Clinic on June 13, 1951, and admitted to the hospital three days later. Although his health had usually been good, he had been subject to attacks of sore throat which were twice complicated by otitis media; the attacks were not associated with evidences of rheumatic, nephritic, or allergic disease. Because of infrequent episodes of lancinating pain, originating in the flanks and radiating anteriorly, his mother took him to a physician in April, 1950. The attacks could not be related to posture or exercise. His heart was found to be enlarged and the arterial pressure elevated. These findings were confirmed in May, 1951, when systolic pressure was about 200 mm. Hg. About this time he experienced morning headaches and difficulty in reading fine print. Results of a symptomatic review were otherwise normal.

There was no history of hypertension or of premature cardiovascular disease in siblings or parents.

His intellectual, emotional, and nutritional status was considered normal. Arterial pressures were 238/160 mm. Hg (left arm) and 256/100 mm. Hg (left leg). The heart sounds were loud and of normal rhythm; the aortic second sound was accentuated, and a Grade II systolic murmur, louder on expiration, was heard at the base. Peripheral pulses were normally palpable. The fundi showed arteriolar constriction (2+), sclerosis (1+), hemorrhages (1+), exudates (1+), and papilledema (2+).

The transverse cardiac diameter was increased to 120% of normal (Ungerleider-Gubner scale), apparently by left ventricular enlargement. An electrocardiogram showed changes considered possibly abnormal (notching of R wave in Lead III, low T waves in Leads AV_L, III, and V_6, and diphasic T wave in Lead V_1). Urographic dye was promptly excreted from both kidneys; the pelviocalyceal systems were considered normal and the ureters somewhat tortuous. The blood urea clearance was 75% of normal. An Addis test yielded urine of maximum specific gravity 1.029, which contained 0.05 gm. of protein per 24 hours and 470,000 red blood cells, 320,000 white blood cells, and 7,000 casts per 12 hours.

Electrophoretic analysis of serum proteins showed total protein to be 9.2 gm.; albumin, 5.0 gm.; alpha-globulin, 0.88 gm.; beta-globulin, 1.08 gm. and gamma-globulin, 1.27 gm., per 100 ml. Peripheral blood showed 4,880,000 red blood cells per cubic millimeter, 13 gm. of hemoglobin per 100 ml., and 12,000 white blood cells per cubic millimeter, with 80% neutrophiles, 9% lymphocytes, 11% monocytes, and 1% eosinophiles.

On the third hospital day the patient had headaches, nausea, and vomiting. Intravenous test doses of piperoxan (benodaine®) hydrochloride transiently increased and those of tetraethylammonium chloride and histamine transiently decreased arterial pressure; the drug-induced variations were about 20/30 mm. Hg in each case. An aortogram (Fig. 1) showed outlines of aorta and renal arteries which were apparently normal; one of the mesenteric arteries was tortuous and of increased size. A study of vascular responsiveness was done with the patient under thiopental (pentothal®) sodium anesthesia at the time of aortography. This study was based on the observations of Page and McCubbin[11] that dogs with neurogenic hypertension

9. Howard, T. L.; Forbes, R. P., and Lipscomb, W. R.: Aneurysm of Left Renal Artery in Child 5 Years Old with Persistent Hypertension, J. Urol. **44**:808-815 (Dec.) 1940.

10. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, J. Urol. **39**:611-626 (May) 1938.

11. Page, I. H., and McCubbin, J. W.: Increased Resistance to Autonomic Ganglionic Blockade by Tetraethylammonium Chloride and Pentamethonium Iodide in Experimental Neurogenic Hypertension, Am. J. Physiol. **168**:208-217 (Jan.) 1952.

show repetitive deep depressor responses to intravenously administered tetraethylammonium chloride, whereas normal and renal hypertensive animals show slighter initial depressor responses, and these, with repeated dosage, became pressor. The responses to tetraethylammonium chloride in this patient were similar to those observed in experimental renal hypertension, in that depressor responses were small initially and soon became pressor.

A low-sodium diet (0.2 gm. of sodium) had been prescribed, and mercurial diuretics were given on admission as a test of the possible effectiveness of sodium restriction. Hexamethonium bromide was given intramuscularly in increasing dosage on succeeding days. Neither measure was effective. Diastolic pressure increased daily by 5 or 10 mm. Hg, and the manifestations of hypertensive encephalopathy became progressively severer.

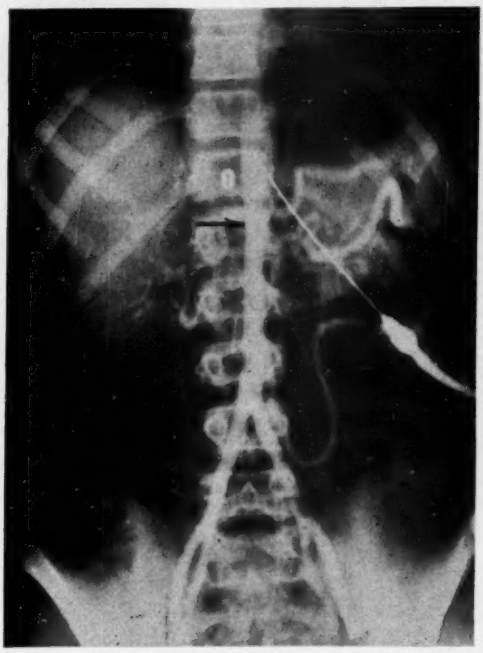

Fig. 1.—Aortogram demonstrating dilated mesenteric arteries. Arrow indicates zone of coarctation.

Review of the data a week after admission showed that neurogenic, endocrine, cardiovascular, and intrarenal causes of hypertension seemed to have been excluded; the age of the patient and the negative family history indicated that the disease was secondary to some ascertainable cause. The renal vasculature seemed to be intact, as evidenced by normal results on tests of renal function and the normal urinary sediment; this, in the face of severe hypertension, suggested that the intrarenal vessels were somehow bilaterally protected from the impact of this pressure, as they are in experimental hypertension due to renal arterial compression. With this and the patient's obviously desperate situation in mind, a laparotomy was advised in the hope of finding some remediable compression of the renal arteries.

Arterial pressure when the patient was under anesthesia was 200/160 mm. Hg. Some of the mesenteric arteries were seen to be enlarged and tortuous; the right kidney was somewhat smaller than the left, and, when it had been mobilized, no pulse was felt in the right renal artery.

The right kidney was removed, and, since blood did not flow through the aortic stump of the renal artery, a probe was passed which met resistance, apparently at the arterial orifice.

Arterial pressure was maintained at about 250/170 mm. Hg postoperatively; retinopathy and encephalopathy increased in severity. The patient died on the fourth postoperative day with evidences of intracerebral bleeding.

Autopsy Observations.—Results of Gross Examination: Heart: The heart weighed 455 gm. The epicardial surface and the coronary arteries were apparently normal; the diameters of the ventricular cavities at two-thirds the distance from the apex were 3 by 2 cm. in the left and 5 by 2 cm. in the right. The wall of the left ventricle was 2.5 cm. in thickness, the interventricular septum, 2.5 cm., and the right ventricle, 7 mm. The myocardium seemed normal, as did the endocardium and valves (circumferences of the valves were as follows: tricuspid, 11 cm.; pulmonary, 6.5 cm.; mitral 9.3 cm., and aortic, 6.2 cm.). The foramen ovale and the ligamentum

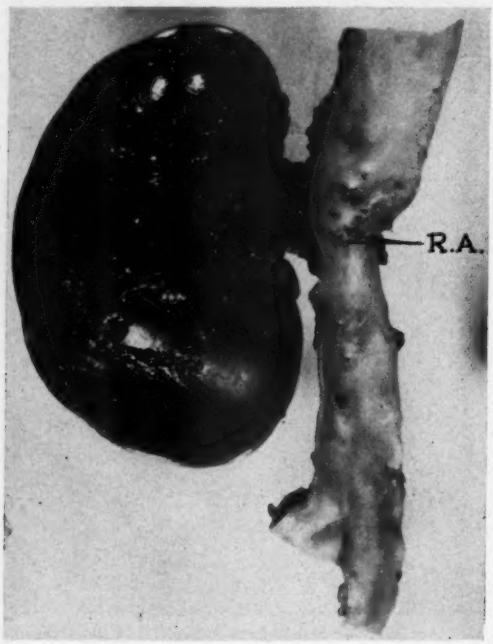

Fig. 2.—Abdominal aorta, opened posteriorly, with left kidney. Note zone of coarctation and narrowed orifices. *R.A.* indicates renal artery orifices.

arteriosum were normally closed. The left coronary orifice was normal; the right coronary orifice took its origin from three grouped apertures 1.5, 1.0, and 0.5 mm. in diameter.

Aorta: The thoracic aorta seemed normal. Diameters were 6 cm. (ascending arch), 4.5 cm. (mid-arch), 4.5 cm. (descending), and 3.7 cm. (upper abdominal). The orifices of thoracic arteries were not remarkable. At a point 1 cm. cephalad to the orifice of the superior mesenteric artery the aorta narrowed (Fig. 2). Its diameter here was 3.4 cm.; at the superior mesenteric orifice, 3.0 cm.; at the adrenal arteries, 2.8 cm., and at the level of the renal arteries, 2.5 cm. The diameter of the aorta then increased to a maximum of 2.8 cm. at the bifurcation. The arterial orifices in the constricted zone were small. The celiac axis appeared as a slit, with a pinpoint aperture; the orifice of the superior mesenteric artery measured 0.5 mm.; the adrenal artery orifices were larger, about 1 mm. in diameter. The long axes of the slit-like orifices of the

renal arteries were directed caudally and laterally by a pad of thickened intima. They admitted a probe of about 0.5-mm. diameter. The stump of the right renal artery contained a recent thrombus. Distal to the orifice the lumen of the left renal artery was of normal size (about 4 mm. in diameter). The orifices of the iliac, lumbar, and inferior mesenteric arteries were not remarkable; the last measured 7 mm. in diameter. The intima in the constricted zone of the aorta was finely nodular, yellow, and linearly streaked.

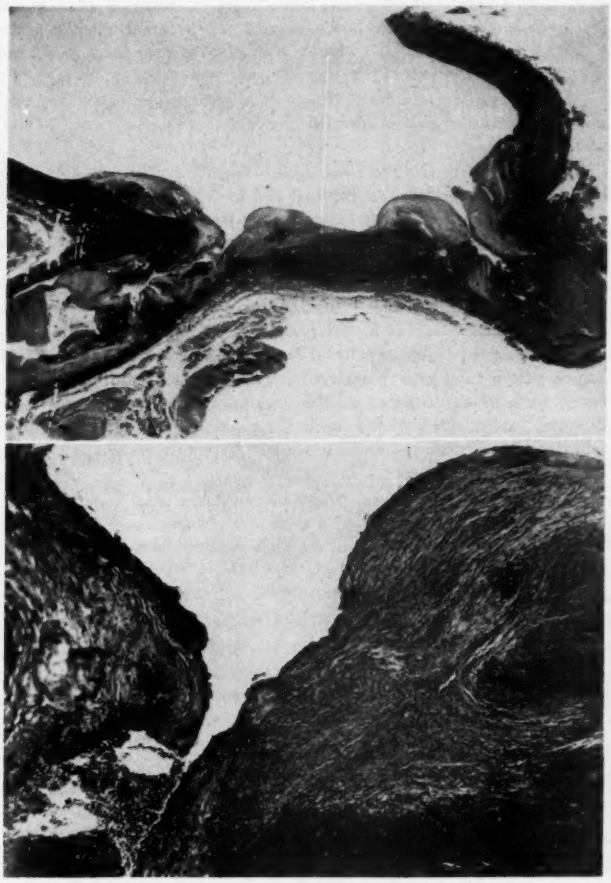

Fig. 3.—Top, photomicrograph of aorta through orifices of renal arteries. Note mound-like projections of intima at orifices and narrowing of proximal portions of renal arteries. × 8. Bottom, photomicrograph of renal orifice, demonstrating thickened intima with a mass of dark-staining (elastic tissue) material in juxtamedial zone. Verhoeff stain; × 50.

Kidneys: The right kidney, which had been removed at operation, weighed 105 gm., measured 8 by 8 by 3 cm., and was grossly normal. The lumen of the renal artery was of normal diameter. The left kidney weighed 120 gm., measured 10 by 5 by 3 cm., and, like the right, was grossly normal.

Brain: The brain weighed 1,600 gm. An area of rostral caudal marking of the uncinate processes (Grade 2 on the right, Grade 1 on the left) indicated compression by the tentorium cerebelli. A small fusiform aneurysm (0.5 mm. in diameter) was found at the junction of the left anterior cerebral and anterior communicating arteries. Coronal section showed a clot 7 by 5 mm. in the head of the caudate nucleus. A zone of hemorrhage (1 by 2 cm.) was found in the region of the left anterior putamen at the level of the optic chiasm; this extended posteriorly and was limited by the external capsule and the inferior posterior limb of the internal capsule. A large lenticulostriate branch of the middle cerebral artery entered it and showed cylindrical dilatation (1 cm. in length and 2 mm. in diameter) 1 cm. from the anterior perforating substance. No rupture could be found. Two areas of liquefaction were found in the right putamen (6 by 7 and 3 by 2 cm.). A branch of the lenticulostriate was traced to this area.

Results of Microscopic Examination: Heart: The myocardium of the left ventricle, right ventricle, and interventricular septum revealed fragmentation of muscle cells with an occasional rectangular cell nucleus.

Aorta: The thoracic aorta was not remarkable. Beginning at the zone of constriction, the intima was thickened by an eosinophilic material and by increased density of connective tissue, especially in the vicinity of the origin of the superior mesenteric artery. These changes persisted at the level of the adrenal arteries. The orifices of the adrenal arteries were patent and their walls normal. Adjoining the aorta were several small arteries showing marked intimal proliferation, with complete obliteration of lumina in some instances. Sections (Fig. 3) at the level of origin of the renal arteries showed that the intima was thickened by a connective tissue deposit, which was especially dense at the artery orifices. Serial sections revealed these cushions to be symmetrically located anterolaterally in the aorta, separated by a median groove. The narrowed orifices of the renal arteries emerged from the midportion of this intimal thickening, which extended for a short distance into the proximal portions of the renal arteries. The media of the aorta, stained with Verhoeff elastic tissue stain, showed only a few masses of elastic tissue adjoining the deeper zone of intimal sclerosis. Adventitial vessels in this area in several instances revealed fibrinoid change.

Kidneys: Glomeruli were well formed and contained the usual quantity of blood. There were no demonstrable tubular changes. No arteriolar changes could be seen in the sections studied. Larger arteries in the fat tissue of the hilus showed slight hypertrophy of their walls. The renal pelves were not remarkable.

Spleen and adrenal gland: The capsular arteries of the adrenal gland showed moderate hypertrophy of their walls. The splenic arterioles were similarly affected.

Brain: Sections of the brain confirmed the gross observations.

Pathologic Diagnoses.—The following were the main pathologic diagnoses: coarctation, congenital, of abdominal aorta (segment extending from immediately above origin of the superior mesenteric arteries to a level beneath the origin of the renal arteries); stenosis, severe of artery orifices (renal, superior mesenteric, celiac axis) due to arteriosclerosis of the fibrous intimal type; cardiac hypertrophy; intercerebral hemorrhage, basal ganglia, left; fusiform aneurysm of lenticulostriate artery, and berry aneurysm at junction of the left anterior cerebral and anterior communicating artery.

COMMENT

The lesions in the zone of coarctation in this case resemble those found by Edwards and co-workers [12] in congenital coarctation of the isthmic aorta. The outstanding observations are intimal thickening by accumulation of relatively acellular collagenous tissue and the presence of masses of elastic tissue concentrated in the region of the media. The intimal lesion in isthmic coarctation is believed to be secondary to the impact of eddy currents on the coarcted zone. In our patient, the

12. Edwards, J. E.; Christensen, N. A.; Clagett, O. T., and McDonald, J. R: Pathologic Considerations in Coarctation of the Aorta, Proc. Staff Meet., Mayo Clin. **23**:324-332 (July 21) 1948.

postulation that the intimal change which effectively stenosed the orifices of the renal arteries is secondary accords with the apparent delay in onset of hypertension and its severe and rapidly progressive course thereafter. Another mechanism of delayed onset of hypertension can be invoked; on the assumption that growth of zones of coarctation does not parallel growth of the body as a whole, the onset of hypertension during the rapid growth and enhanced metabolism characteristic of adolescence would correspond with the delayed onset of renal hypertension in growing rabbits after ligatures had been loosely placed around the renal arteries in early life.[13] In either case, increased arterial pressure would tend to sustain renal blood flow and maintain excretory function against the orificial increase in renal arterial resistance, while the orificial stenosis would tend to protect the renal arterioles.

Coarctation of the abdominal aorta is so rare that Kondo and associates [14] were able to find only eight reported cases. At autopsy, their patient, a 12-year-old girl, showed diffuse aortic atherosclerosis, as well as the jet lesion of Edwards and colleagues [12] in the coarcted segment. Associated hypoplasia of peripheral vessels so damped peripheral pulses that estimates of arterial pressure were not possible. That hypertension was present was indicated by cardiac hypertrophy. Its nature and relation to renal circulation were not demonstrated, but a mechanical basis in the increased peripheral resistance occasioned by hypoplasia of the large arteries can be postulated. One other patient, a 58-year-old man, has been reported [15] as exhibiting the coincidence of arterial hypertension and coarctation of the abdominal aorta. The description of the abdominal aorta is consistent with an origin of the lesion in a healed dissecting aneurysm. Hypertension in this case was considered to be due to restriction of renal arterial flow. However, the intrarenal arterioles were hypertrophied; this, the patient's age, and the possible nature of the lesion suggest that the hypertension was primarily "essential."

Both in coarctation of the isthmus of the aorta and in the case of Kondo and co-workers [14] of coarctation of the abdominal aorta with peripheral arterial hypoplasia, arterial hypertension seems to be in part a mechanical result of increased resistance at sites of aortic or arterial stenosis. However, in the case here described, the absence of any considerable aortic stenosis in the zone of coarctation indicates that the hypertension was a result of stenosis of the renal arteries and, therefore, humorally mediated.

The findings in this case suggest that antemortem diagnosis of this presently unique condition is possible. Had the condition been recognized, transplantation of the kidney to another, unimpeded arterial circulation might conceivably have been lifesaving. Symptomatically, the attacks of recurrent abdominal pain could be construed as evidences of renal ischemia consequent on transient displacement of these organs; such ischemia was observed in the right kidney at operation. The significance of seemingly complete preservation of intrarenal vessels in the face of

13. Drury, D. R.: Production by New Method of Renal Insufficiency and Hypertension in Rabbit, J. Exper. Med. **68**:693-701 (Nov.) 1938.

14 Kondo, B.; Winsor, T.; Raulston, B. O., and Kuroiwa, D.: Congenital Coarctation of Abdominal Aorta, Theoretically Reversible Type of Cardiac Disease, Am. Heart J. **39**:306-313 (Feb.) 1950.

15. Wang, H. W.: Hypertension in Circumscribed Stenosis of Abdominal Aorta, Cardiologia **15**:30-35, 1949.

severe hypertension as evidence of bilateral renal arterial obstruction is noted above. The dilated mesenteric arteries observed in the aortogram and at operation, and ascribed at autopsy to hypertrophy of the left colic artery, are evidence of stenosis and formation of collateral vessels in the mesenteric circulation. Lastly, a careful review of the aortogram after autopsy showed some narrowing of the aorta in the coarcted zone.

SUMMARY

The syndrome of malignant hypertension resulting from stenosis of the aortic orifices of the main renal arteries is reported in a 14-year-old boy. The stenosis was part of the lesion of coarctation of the abdominal aorta. Associated vascular anomalies indicate that the lesion was congenital.

The possibility of antemortem diagnosis and operative relief of this presently unique condition is suggested.

ADDENDUM

After this manuscript was completed, a case of coarctation of the abdominal aorta simulating pheochromocytoma was reported.[16] The hypertension of this 45-year-old patient was paroxysmal; the urine was free of albumin; the lesion was observed during exploration of the left adrenal region with left adrenalectomy.

16. Goldzieher, J. W.; McMahon, H. E., and Goldzieher, M. A.: Coarctation of the Abdominal Aorta Simulating Pheochromocytoma, A. M. A. Arch. Int. Med. **88**:835-839 (Dec.) 1951.

ISLET-CELL ADENOMA OF THE PANCREAS

Metabolic Studies on a Patient Treated with Corticotropin and Cortisone

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ALTHOUGH the diagnosis of pancreatic-cell adenoma is no longer a medical curiosity, the entity is still rare, only about 400 cases having been reported to date.[1] Moreover, the syndrome is important because it offers some clue to a more complete understanding of carbohydrate metabolism. The observation that the administration of corticotropin (ACTH) or of cortisone can correct the hypoglycemia of pancreatic hyperinsulinism [2] has raised the problem of the physiological mechanism of action of the hormones. The studies on our patient are germane to this problem.

REPORT OF A CASE

W. J. H. was a 58-year-old American Legion representative, who was admitted to the Salt Lake Veterans Administration Hospital on Jan. 8, 1951, for evaluation of attacks of bizarre behavior. In 1944 the patient first noticed incoordination of his hands when engaged in prolonged work. This was attributed to nervousness. During the next two years he had endured frequent episodes of incoordination while driving, requiring him to stop. Relief was obtained by rest and nourishment. He even took to carrying candy for the relief of his symptoms.

In 1947 he had several episodes of diplopia, and one morning before breakfast he became maniacal and ran about his room yelling and pounding the walls. He was hospitalized for 21 days at this time, with a diagnosis of "psychoneurosis, anxiety state, moderate with conversion symptoms." Laboratory studies on this admission showed a fasting blood sugar level of 65 mg. per 100 ml. (method not stated). The spinal fluid findings were normal, as was the electroencephalogram. After discharge the patient continued to note during long drives episodes of

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1. Howard, J. M.; Moss, N. H., and Rhoads, J. E.: Collective Review: Hyperinsulinism and Islet Cell Tumors of the Pancreas with 398 Recorded Tumors, Internat. Abstr. Surg. **90**:417, 1950; in Surg., Gynec. & Obst., May, 1950.

2. McQuarrie, I.; Ziegler, M. R.; Wright, W. S.; Bauer, E. G., and Ulstrom, R. A.: Further Studies on the Effects of ACTH on Spontaneous Hypoglycemosis, in Proceedings of the Second Clinical ACTH Conference, Vol. II: Therapeutics, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, pp. 69-80.

incoordination and diplopia, which he relieved by taking a cup of coffee with sugar. It is interesting that at this time he was using large amounts of 1% epinephrine by nebulizer for the relief of asthma, which he had had for more than 30 years.

In October, 1948, he consulted another physician, and an oral dextrose-tolerance test revealed the following blood sugar values: 50 mg. per 100 ml. on fasting; 55 mg. at one hour; 31 mg. at two hours; 48 mg. at three hours; 48 mg. at four hours, and 67 mg. at five hours. The patient was told that he had hypoglycemia and was instructed to take frequent feedings and to carry food for the prevention and relief of his symptoms.

His symptoms increased in frequency, however; paresthesia of the extremities developed, and he had "black-out spells," during which he would faint on the street. On several occasions he drove his car considerable distances and had no recollection of how he had arrived there.

In 1950 he had to quit driving because of his unpredictable behavior. He then noted that the omission of a midmorning feeding resulted in an episode of maniacal behavior. The patient could recall his actions but had no control over them. He always obtained partial relief of symptoms within five minutes after the ingestion of fruit juices. On several occasions he collapsed on the street and was taken to the hospital but recovered by the time he reached the hospital. The patient finally appreciated the necessity of eating his breakfast immediately upon arising and

TABLE 1.—*Results of Control Studies*

Dextrose-Tolerance Test (Figs. 1 and 2)							
Time, min.	0	30	60	120	180	240	300
Mg. glucose/100 ml. blood after ingestion of 100 gm. dextrose	20	36	28	28	28	..	..
Mg. glucose/100 ml. blood after intravenous administration of 0.5 gm. dextrose per kg. body weight over 20 min.	25	83	12.5	21	25	21	25
Response to Epinephrine (Fig. 3)							
Time, min.	0	15	30	45	60	300	..
Mg. glucose/100 ml. blood after intramuscular administration of 0.1 mg. epinephrine per 10 kg. body weight	31	78	98	104	122	..	..
Absolute eosinophile count per cu. mm. blood	269	..	69	..	..	162	..
Response to 30 Mg. of Corticotropin Given Intramuscularly							
Time, min.	0	60	120	180	240	..	..
Mg. glucose/100 ml. blood after corticotropin administration	36	36	44	40	40	..	..
Absolute eosinophile count per cu. mm. blood	156	..	..	..	38	..	..

before undertaking any activity, and also his need for frequent feedings to prevent the attacks. In the two years prior to admission his weight rose from 155 to 187 lb. (70.3 to 84.8 kg.).

Results of Physical Examination.—The temperature, pulse rate, and respiration rate were normal. The blood pressure was 110/70. The patient was a somewhat obese man whose physical findings were not remarkable, save for acne rosacea and asthmatic breath sounds.

Results of Laboratory Studies.—His urine was normal and concentrated to a specific gravity of 1.022 on routine specimens. The volume of packed red blood cells was 49 ml. per 100 ml., and the white blood cell count was 9,500, with a normal differential count. Four to 5% of the leucocytes were eosinophiles. During the period of study his fasting blood sugar values by the Somogyi-Nelson method [3] were 38, 20, 25, 31, and 29 mg. per 100 ml. Results of liver-function tests, including the van den Bergh test and determination of thymol turbidity, urinary urobilinogen excretion, sulfobromophthalein (bromsulphalein®) sodium retention, and prothrombin time, were normal. Roentgenographic studies of his chest showed a small area of thickened pleura near the heart; the flat plate of his abdomen disclosed no pancreatic calcification. The appearance on a gastrointestinal series was not remarkable. The urine 17-ketosteroid output was 11.4 mg. per 24 hours.

After the control studies, the patient was given 30 mg. of corticotropin intramuscularly every six hours for five days, during which time his fasting blood sugar ranged from 90 to 115 mg.

3. Nelson, N.: A Photometric Adaptation of the Somogyi Method for the Determination of Glucose, J. Biol. Chem. **153**:375, 1944.

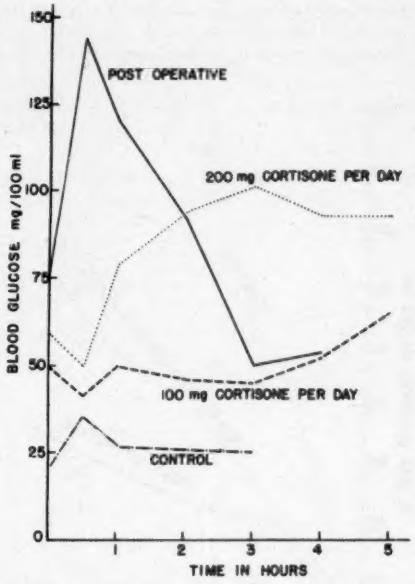

Fig. 1.—Blood sugar levels on oral dextrose-tolerance test with 100 gm. of dextrose, showing effect of cortisone therapy and removal of adenoma. Note the decreased dextrose tolerance with the larger dose of cortisone.

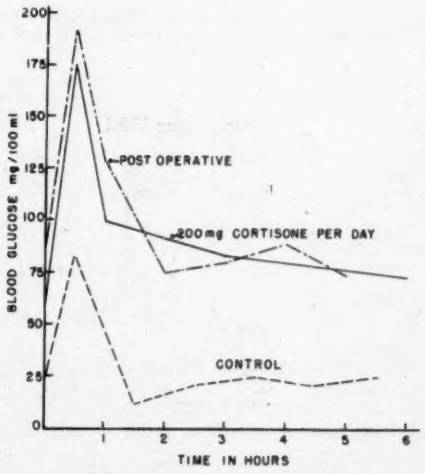

Fig. 2.—Blood sugar levels on intravenous dextrose-tolerance test with 0.5 gm. of dextrose per kilogram of body weight, showing effects of cortisone therapy and of removal of adenoma.

per 100 ml. While the patient was receiving corticotropin, the serum potassium level dropped from 4.0 mEq. per liter on Feb. 1 to 3.2 mEq. on Feb. 5. Dryness of the mouth and abdominal cramps developed, both of which cleared after the administration of 4 gm. of potassium chloride

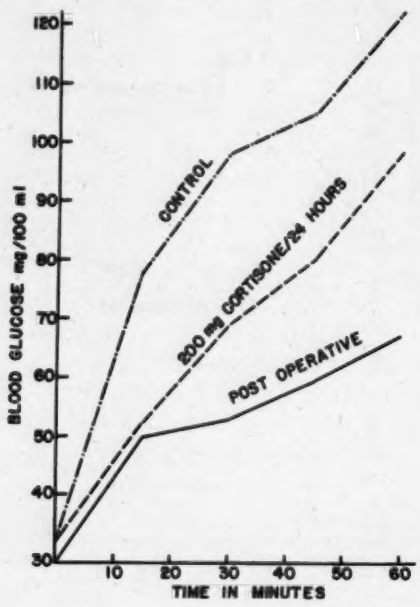

Fig. 3.—Blood glucose response to administration of 0.1 mg. of epinephrine per 10 kg. of body weight. Cortisone and postoperative curves were begun one hour after the injection of insulin.

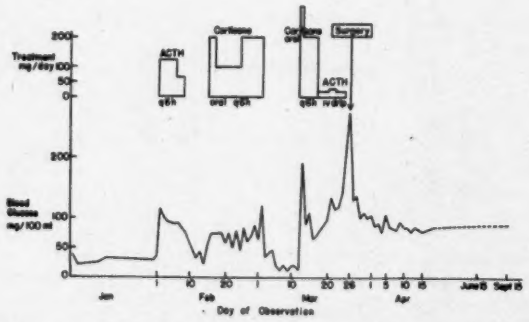

Fig. 4.—Summary chart showing effect of treatment on patient's blood sugar level.

per day. After several days of potassium therapy, the serum potassium value rose to the previous levels. There was no change in the potassium content of the red blood cells.

The dosage of corticotropin was then reduced to 15 mg. every six hours for two days. This was associated with some lowering of the previous blood sugar levels but not to the hypoglycemic range. The medication was discontinued for seven days, during which time the patient

was given placebos. Within four days his fasting blood sugar dropped to 32 mg. per 100 ml., and his paresthesias and feelings of incoordination returned. He was then given 200 mg. of cortisone acetate daily by mouth, in four divided doses; this was followed by a prompt rise in his fasting blood sugar to between 54 and 73 mg. per 100 ml. and improvement of his symptoms. The cortisone dose was reduced to 100 mg. daily for seven days and then raised to 200 mg. again. Blood sugar levels were maintained within the normal range on this regimen, although the average blood sugar levels were somewhat higher at the higher doses (Fig. 4). While the

TABLE 2.—*Results of Dextrose-Tolerance Tests During Cortisone Therapy (Figs. 1 and 2)*

Time, min.	0	30	60	120	180	240	300	360
Mg. glucose/100 ml. blood while receiving 100 mg. cortisone orally (after ingestion of 100 gm. dextrose)	50	46	50	46	46	54	67	..
Mg. glucose/100 ml. blood while receiving 200 mg. cortisone orally (after ingestion of 100 gm. dextrose)	61	50	79	94	102	94	94	..
Mg. glucose/100 ml. blood while receiving 200 mg. cortisone orally (after intravenous administration of 0.5 gm. glucose/kg. body weight over 20-min. period)	58	175	100	92	83	81	77	73

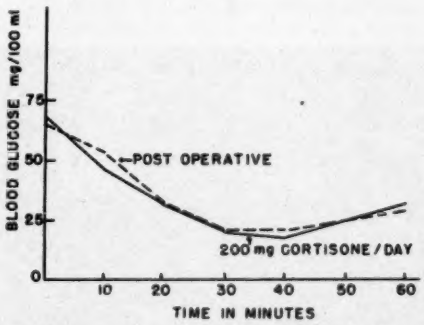

Fig. 5.—Response of blood sugar level to insulin-tolerance test with 0.1 unit of insulin per kilogram of body weight during cortisone therapy and after removal of adenoma of pancreas. No test was done during control period because of existing hypoglycemia.

patient was receiving cortisone, the dextrose-tolerance tests were repeated (Table 2). While the patient was receiving 200 mg. of cortisone per day, an insulin-tolerance test was done, with administration of 0.1 unit of insulin per kilogram of body weight intravenously. At 0 minutes blood glucose measured 68 mg. per 100 ml.; at 10 minutes, 46 mg.; at 20 minutes, 32 mg.; at 30 minutes, 20 mg.; at 40 minutes, 18 mg., and at 60 minutes, 32 mg. (Fig. 5). At 60 minutes he was given epinephrine as before, and the blood sugar levels were measured at the stated periods with the following results: At 0 minutes blood glucose was 32 mg. per 100 ml.; at 15 minutes, 52 mg.; at 30 minutes, 68 mg.; at 45 minutes, 80 mg., and at 60 minutes, 98 mg. (Fig. 3).

The patient was then given a constant diet to determine his nitrogen balance. During this period his fasting blood sugar values ranged from 10 to 23 mg. per 100 ml. He was then given 200 mg. of cortisone acetate daily, and, after the first day of treatment, his blood sugar levels were again within the normal range. With cortisone therapy his average nitrogen excretion rose to 18.6 gm. per day, as compared with 14.5 gm. per day during the control period. His daily nitrogen intake was about 16.5 gm.

Upon completion of the nitrogen balance study, the patient was given 15 mg. of corticotropin each day by slow intravenous drip over a period of 12 to 16 hours. This treatment maintained his fasting blood sugar at between 64 and 110 mg. per 100 ml.

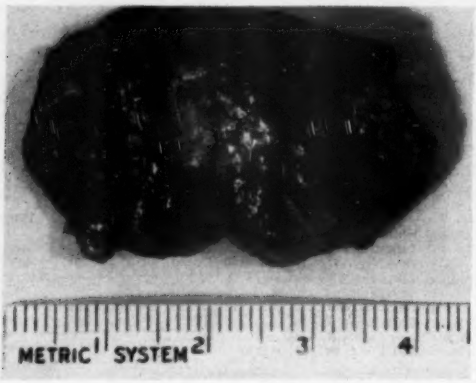

Fig. 6.—Gross appearance of adenoma after removal. Gland has been opened to show lobular structure.

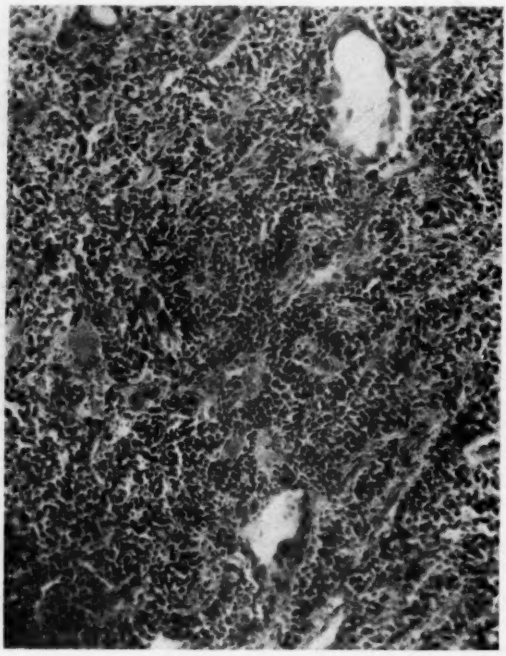

Fig. 7.—Photomicrograph of islet-cell tumor. Frozen section stained with hematoxylin and eosin and magnified 106 times. Note the uniform small cell pattern and prominent orientation of the small cells around blood vessels.

On March 26, an exploratory operation was performed by Dr. J. A. Gubler, Chief of the Surgical Service, Veterans Administration Hospital, and a soft mass was found in the region of the uncinate process of the pancreas. The mass upon removal measured 2.8 by 2.3 by 1.9 cm. and weighed 6 gm. (Fig. 6). Pathological study revealed the mass to be an islet-cell adenoma of the pancreas, (Fig. 7). Unfortunately, a bioassay for the insulin content of the mass could not be made. At the operation a biopsy specimen of the liver was removed and observed to be normal histologically. The patient's postoperative course was uneventful. On the day of operation the blood sugar rose to a peak of 274 mg. per 100 ml., but thereafter it was within the normal range.

Subsequently, the oral and intravenous dextrose-tolerance tests and tests of the response to insulin and epinephrine were repeated. The results are shown in Table 3.

The patient was last seen about six months after his operation, at which time his blood sugar was still normal and he was quite asymptomatic.

COMMENT

This case raises an interesting problem in carbohydrate homeostasis. In the normal person hypoglycemia will stimulate the adrenal medulla to discharge epi-

TABLE 3.—*Results of Studies After Removal of Adenoma*

Dextrose-Tolerance Test (Figs. 1 and 2)							
Time, min.	0	30	60	120	180	240	300
Mg. glucose/100 ml. blood after ingestion of 100 gm. dextrose	76	144	120	92	48	54	..
Mg. glucose/100 ml. blood after intravenous administration of 0.5 gm. dextrose/kg. body weight over 20 min.	84	192	128	76	80	88	76
Insulin-Tolerance Test (Fig. 5)							
Time, min.	0	10	20	30	40	60	..
Mg. glucose/100 ml. blood after intravenous administration of 0.1 unit insulin/kg. body weight	67	54	33	21	21	29	..
Epinephrine Response (Fig. 3)							
Time, min.	0	15	30	45	60	..	..
Mg. glucose/100 ml. blood after intramuscular administration of 0.1 mg. epinephrine/10 kg. body weight	29	50	53	58	67	..	..

nephrine, which in turn mobilizes glucose from the liver, resulting in a sharp rise in the blood sugar level. The secretions of the adrenal cortex also play a part in restoring the blood sugar level to normal but act more slowly and probably by decreasing the peripheral utilization of the glucose.

In our patient the fundamental difficulty was an oversupply of insulin. Although the tumor was not assayed in this instance, other adenomas have shown a markedly increased insulin content.[4] The hypersecretion of insulin was not counteracted by the usual physiological mechanisms, although the various organs involved in carbohydrate homeostasis were shown to have normal function. The pituitary apparently functioned normally, as shown by the lack of signs of hypopituitarism and by the ability of the adenohypophysis to respond to epinephrine stimulation by effecting a drop in the eosinophile count through the mediation of the adrenal cortex. The liver was normal on biopsy and function tests and in its ability to liberate glucose on epinephrine stimulation. The adrenal cortex showed no involvement, as judged by the normal 17-ketosteroid excretion and an eosinophile drop of 76% on corticotropin stimulation. Although the patient could correct his

4. Marble, A., and McKittrick, L. S.: Islet-Cell Tumor of the Pancreas with Hyperinsulinism: Report of 6 Cases, New England J. Med. **235**:637, 1946.

hypoglycemia when corticotropin, cortisone, or epinephrine was supplied exogenously, the endogenous mechanisms concerned with the maintenance of the blood sugar level were incapable of completely counteracting the excessive secretion of insulin.

Why the pituitary adrenocortical system does not respond to the stress of chronic hypoglycemia resulting from excess insulin by secreting cortical hormone at a rate adequate to maintain the blood sugar level is a most fundamental problem. The hypoglycemia in this patient was corrected by as little as 15 mg. of corticotropin per day supplied exogenously; in contrast, it is probable that his own pituitary was capable of supplying many times this amount of the hormone. Burns and associates reported data which suggest that the human pituitary can elaborate as much as 10 mg. of corticotropin in a few hours.[5] Perhaps the body economy will not allow a state of hypercorticalism to correct an imbalance in one segment of its physiology to the detriment of other body systems, e. g., fluid and electrolyte compartments, antigen-antibody reactions, and protein metabolism. Except for the few situations in which an actual deficiency exists, as in hypopituitarism and in Addison's disease, all our successful therapeutic efforts with corticotropin and cortisone produce hypercorticalism. The hypercorticalism may correct the disease symptoms, but usually other physiological aberrations are produced which are at least potentially detrimental to the organism. It seems that the mechanism controlling the secretion of corticotropin and corticoids involves a balance and that the corticotropin secretion falls when the corticoid level rises, while the corticotropin secretion increases when the corticoid level falls.[6] According to this thesis, the healthy pituitary adrenocortical system is a self-regulating mechanism which makes impossible prolonged endogenous hypercorticalism. The development of methods for measuring the level of circulating corticotropin and adrenocortical hormone will aid considerably in clarifying this point.[7]

It is well established that corticotropin or cortisone can cause an elevation of the blood sugar and a decreased dextrose tolerance. Part of this effect may be due to the increased protein breakdown, but, as was shown in this patient, the catabolic effect of corticotropin or cortisone is a minor factor in the alleviation of the hypoglycemia. During the control period the nitrogen excretion averaged 14.5 gm. per day, and while the patient was receiving 200 mg. of cortisone daily the excretion rose to 18.6 gm. per day. The increase in nitrogen excretion of 4.1 gm. per day would represent the destruction of about 25.6 gm. of protein (4.1×6.25). The destruction of an extra 25.6 gm. of protein is equivalent to the production of about 15 gm. of carbohydrate. It is obvious that this extra amount of carbohydrate available per 24 hours from the protein catabolic effect of cortisone could not explain the rise in blood sugar to normal level when compared with the minimal effect of 100 gm. of dextrose during a dextrose-tolerance

5. Burns, T. W.; Merkin, M.; Sayers, M. A., and Sayers, G.: Concentration of Adrenocorticotrophic Hormone in Rat, Porcine and Human Pituitary Tissue, Endocrinology **44**:439, 1949.

6. Sayers, G.: The Adrenal Cortex and Homeostasis, Physiol. Rev. **30**:241, 1950.

7. Nelson, D. H.; Samuels, L. T.; Willardson, D. G., and Tyler, F. H.: The Levels of 17-Hydroxycorticosteroids in Peripheral Blood of Human Subjects, J. Clin. Endocrinol. **11**:1021, 1951.

test. Furthermore, Conn and his associates [8] found that the change in the blood sugar levels or dextrose tolerance was not necessarily related in time or degree to the loss of body protein in subjects receiving corticotropin. Thus, the alleviation of the hypoglycemia must depend upon some other mode of action of the adrenocortical hormone. Unfortunately, this mechanism has not yet been explained.

Since the temporary diabetes produced by corticotropin or cortisone is relatively insensitive to insulin, it is likely that the beneficial effect of the hormones on insulin hypoglycemia is due to an antagonism to the insulin effect in the periphery rather than to a decreased production of insulin by the pancreatic adenoma. In fact, Kendall [9] could demonstrate the hyperglycemic effect of cortisone in the depancreatized animal, in which insulin production could not play a role. It is noteworthy that administration of 0.1 unit of insulin per kilogram of body weight produced a marked fall in blood sugar in our patient even while he was receiving 200 mg. of cortisone daily (Fig. 5). The curve is essentially normal except for the failure of the usually prompt hypoglycemic response to appear.

This case also illustrates the efficacy of corticotropin given in relatively small doses by slow intravenous administration. A dose of 15 mg. administered intravenously over 12 to 16 hours had a greater hyperglycemic effect than 120 mg. of corticotropin given in four divided doses intramuscularly (Fig. 4).

It was also noted that after cortisone treatment was discontinued the hypoglycemia returned within 24 hours, whereas after cessation of corticotropin therapy the hypoglycemia did not return for several days. Likewise, the blood sugar level was considerably lower after cessation of cortisone therapy than it was after corticotropin treatment was discontinued (Fig. 4). This study is another example of the depression of adrenocortical activity by exogenous cortisone depressing the output of corticotropin. While the cortisone is being administered, the diminished function of the pituitary and adrenal cortex is masked, and signs of hypocorticalism appear promptly upon the discontinuance of cortisone therapy.

To our knowledge, three other cases of pancreatic islet-cell adenoma with corticotropin treatment have been reported.[10] In the case reported by Brown [10b] the hypoglycemia was not completely corrected, but the author probably did not employ a sufficiently high dose of corticotropin.

It is of interest that our patient was able to carry on despite severe hypoglycemia for about seven years. This ability was probably due to the happy coincidence that he suffered from bronchial asthma and used large amounts of 1% epinephrine by nebulizer. As shown by his clinical response and the studies of Conn and Conn,[11] epinephrine is a useful adjunct in the relief of hypoglycemia.

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8. Conn, J. W.; Louis, L. H., and Wheeler, C. E.: Production of Temporary Diabetes Mellitus in Man with Pituitary Adrenocorticotropic Hormone: Relation to Uric Acid Metabolism, J. Lab. & Clin. Med. **33**:651, 1948.

9. Kendall, E. C.: Hormones of the Adrenal Cortex, Endocrinology **30**:853, 1942.

10. (*a*) McQuarrie and others.[2] (*b*) Brown, G. M.: The Effect of ACTH in a Case of Beta Islet Cell Adenoma of the Pancreas, Am. J. Digest. Dis. **18**:145, 1951.

11. Conn, J. W., and Conn, E. S.: Metabolism in Organic Hyperinsulinism: II. Effects of Epinephrine on Glycemic Level and on Combustion of Carbohydrate, Arch. Int. Med. **68**:1105 (Dec.) 1941.

To conclude, corticotropin and cortisone were shown to have a remarkable ability to relieve hypoglycemia in a subject with an islet-cell adenoma of the pancreas. Such treatment is advocated only until the condition can be relieved surgically.

SUMMARY

A 58-year-old man with hypoglycemia of eight years' duration secondary to an islet-cell adenoma of the pancreas was successfully treated with corticotropin and cortisone prior to operation.

The results of oral and intravenous dextrose-tolerance tests and insulin- and epinephrine-tolerance tests during the control, treatment, and postoperative periods are reported.

The results of nitrogen balance studies during cortisone therapy indicate that the correction of hypoglycemia could not be attributed to the protein catabolic effect of the cortisone and was due presumably to an anti-insulin effect in the tissues.

The role of the pituitary adrenocortical system in carbohydrate homeostasis is discussed.

Dr. F. C. Gunn and Dr. O. N. Rambo, of the Pathology Department, supplied the photographs for Figures 6 and 7.

"RE-FORMED GALL BLADDER" WITH STONES FOLLOWING CHOLECYSTECTOMY SEVENTEEN YEARS AGO

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AND
SAUL F. LIVINGSTON, M.D.
BROOKLYN

THE REAPPEARANCE of abdominal symptoms following cholecystectomy frequently provides a source of distress to both the patient and the physician. Dependent upon the lapse of time between the surgical procedure and the onset of symptoms, various diagnoses, such as postcholecystectomy syndrome, spasm of or stones in the common duct, stricture or angulation of the extrahepatic ducts, chronic hepatitis, chronic pancreatitis, and neurogenic factors, are lightly proffered without adequate substantiation, and usually symptomatic therapy is instituted. While these may represent the disorders following gall-bladder surgery, other factors not commonly apparent to the physician at the time may play an integral part in the redevelopment of the symptom complex. A careful history and physical examination augmented by a detailed description of the surgical procedure and findings at the time of the operation will often lead to a clearer understanding of the underlying pathological changes. The proper assessment of the many potential alterations in the postoperative biliary tract is essential to the intelligent management of the patient. While the entity of "re-formed gall bladder" following cholecystectomy is not entirely unknown to the medical literature, its frequency and subsequent misdiagnosis serve to demonstrate that this concept has not been adequately popularized. The following case will serve as an example.

REPORT OF CASE

Y. B., aged 46 years, had a cholecystectomy in April, 1935. A description of the operation revealed that the gall bladder was distended, measuring about 12 cm. in length, thickened, and acutely inflamed and contained many stones. A cholecystectomy was performed from the fundus downward, exposing the cystic duct, which was clamped, cut between clamps, and tied. The cystic artery was exposed and cut between two ties.

The pathologist's diagnosis was "acute ulcerative cholecystitis with cholelithiasis (46 stones)." The patient had a normal postoperative course and was discharged from the hospital.

She had no complaints referable to the gall-bladder operation until November, 1943, or eight years later, when for the first time she began to experience vague pain in the right lower abdominal quadrant and midback. This symptom became more progressive, and on April 2, 1946, she had a severe exacerbation, the pain appearing first in the right lower abdominal quadrant and at times radiating to the right flank. It was intermittent and associated with nausea. The rectal temperature at the time was 102 F. Physical examination revealed no evident gross abnormality. The abdomen was soft, and no masses were palpated. The scar of the previous operation was well healed, and there was no evidence of a hernia. She was treated symptomatically, and the temperature returned to normal within 24 hours. Because of the persistence of back pain, a urological survey was performed on April 27, 1946. Urinalysis revealed a specific gravity of 1.018; the reactions for sugar and albumin were negative, and the specimen showed no

abnormalities on microscopic examination. A flat plate of the abdomen was negative for calculi. An intravenous pyelogram demonstrated both kidneys to be normal in size, shape, position, and function.

The patient was not seen again until Jan. 28, 1950. At this time she stated that she had been symptom free for the past two years. Recently, she began to experience colicky-type pain starting to the right of the umbilicus or directly over the lower angle of the scar in the right upper abdominal quadrant. This pain would radiate around to the back and sometimes down to the right groin. These attacks would cause her to double up, and relief was obtained only by

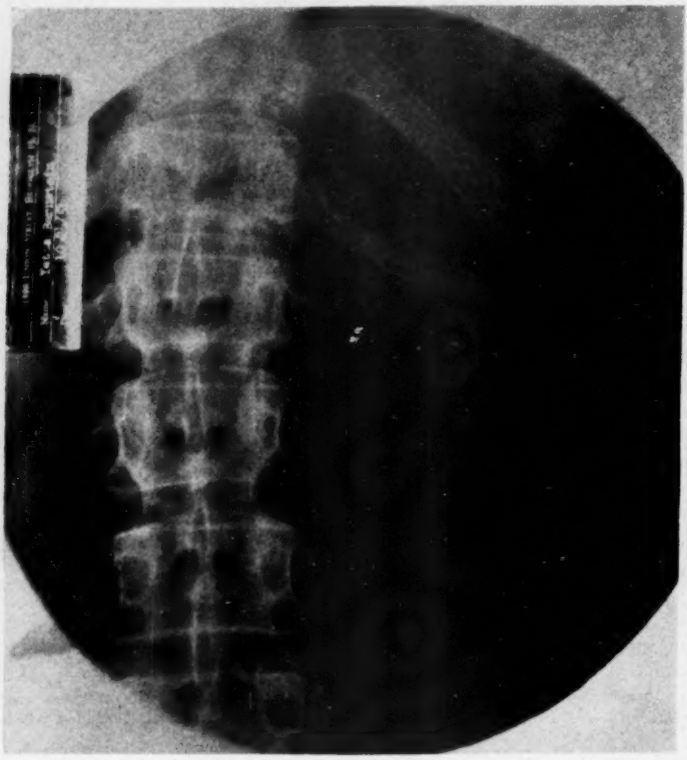

Fig. 1.—Spot cone-down study, showing the faintly calcific shadows of a facetted nature.

hypodermic injection of morphine. These attacks were not accompanied with chills, fever, or any urinary symptoms. She definitely stated that these attacks were not like those she had experienced before the gall-bladder operation. Careful physical examination again revealed no definite cause for these attacks. On Feb. 11, 1950, roentgenographic examination was done to include the right upper abdominal quadrant and the pancreatic region. It failed to reveal any evidence of calculi. This was followed with a complete gastrointestinal survey on March 11. No abnormalities were found. She was then given antispasmodic drugs, with some subsequent relief, but she continued to have mild attacks at less frequent intervals. In August, 1951, the attacks became severer and required use of opiates for the relief of pain. About this time, the pain became more or less continuous.

On Oct. 29, 1951, complete gastrointestinal roentgenologic study was repeated and found to be normal. However, a cluster of faint shadows with calcific rims was seen about 1 in. (2.5 cm.) to the right of the transverse process of the second lumbar vertebra. A gall-bladder series failed to visualize the biliary sac. On numerous spot cone-down studies, the faintly calcific shadows of a facetted nature were again identified. These shadows were regarded as suggestive of recurrent gallstones (Fig. 1).

She was admitted to the Jewish Hospital of Brooklyn on Nov. 17, 1951. Results of physical examination were entirely normal. There was no icterus, and the stools were of normal color.

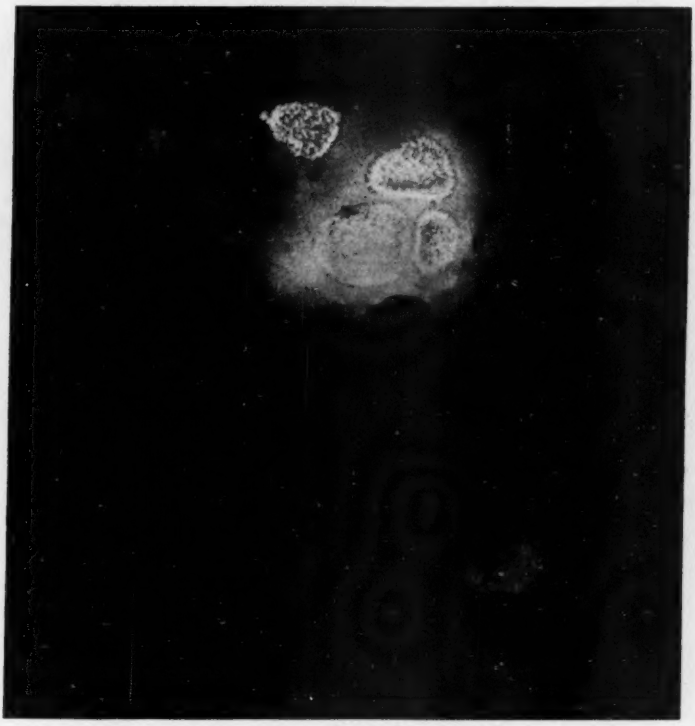

Fig. 2.—Roentgenogram of the removed "re-formed gall bladder" with calculi within. At the bottom is the black amorphous calculus-like material from the common duct.

Urinalysis revealed a specific gravity of 1.012, an acid reaction, and negative reactions for sugar and albumin; a few epithelial cells were seen on microscopic examination. A blood count disclosed a hemoglobin concentration of 81% and 6,050 white blood cells, with 47 polymorphonuclear cells, 4 band cells, 46 lymphocytes, 2 monocytes, and 1 eosinophile. The Mazzini reaction was negative. Cephalin flocculation was normal. The thymol-turbidity test showed 2.7 Maclagan units. Blood chemical values were reported as follows: The icterus index was 10. Direct serum bilirubin was 0.3 mg. and total serum bilirubin was 0.4 mg. per 100 cc. Direct serum bilirubin was 75% of total bilirubin. Amylase measured 111 mg. Total cholesterol was 150 mg. and free cholesterol 35 mg. per 100 cc. The percentage of free cholesterol was 23. Total protein was 7.8 gm. per 100 cc., with 4.4 gm. of albumin and 3.4 gm. of globulin. Sugar was 92 mg.; calcium, 9.6 mg.; phosphorus, 3.6 mg., and urea nitrogen, 24 mg., per 100 cc.

On Nov. 23, an exploratory operation was performed. A sac-like structure was found in the region of the previous gall-bladder bed, covered by and adherent to the duodenum. This structure, when freed from its surrounding adhesions, measured about 7 by 3 cm. and contained several calculi. Aspiration of this sac revealed yellow bile-stained fluid. The terminal end of the sac was tortuous and emptied into a dilated common duct. The "re-formed gall bladder" was removed and tied flush with the common duct. The common duct was then explored, and some black amorphous calculus-like material was removed (Fig. 2).

Ten days after operation, a retrograde cholangiogram was performed. There was marked distention of the common duct and part of the intrahepatic ducts. The transition between the dilated portion of the duct and the intrahepatic secondary radicles was quite sudden. The

Fig. 3.—Microscopic section of the "re-formed gall bladder" showing glands in the mucosa representing ectasia of the terminal portion of the cystic duct.

distal end of the common duct on the immediate films assumed a rather square configuration, but within five minutes it tapered down normally and the dye could be seen entering the duodenal loop. No filling defect was noted within the common duct or the biliary radicles.

The pathologist's report was as follows: Grossly the "gall bladder" measured 7 by 3 cm. (Fig. 2). The serosa was pink-tan, smooth, glistening, and covered with fibrous tissue tags. The lumen contained 1 cc. of brown bile, together with four calculi measuring 0.7 to 1.0 cm. in diameter. The mucosa was tan-brown and trabeculated. The wall measured 0.1 cm. in thickness.

Microscopically the preparation showed the surface to be partly covered by well-preserved tall columnar cells. Within the lamina propria, in some areas, many glands were noted. The

muscular coat was broad and in places showed a scattering of inflammatory cells and extravasated blood. With the presence of glands in the mucosa, this probably was representative of an ectasia of the terminal portion of the cystic duct (Fig. 3).

The patient was discharged from the hospital on Dec. 6, 1951, and has been asymptomatic since.

COMMENT

The term "re-formed gall bladder" following cholecystectomy was first used by Beye [1] in 1936 to designate a clinical syndrome rather than a pathological entity. In the majority of cases reported in the literature, the development of a pouch simulating a gall bladder was usually due to dilatation of the cystic duct stump following ineffectual surgical removal. In only a few instances recorded was there redevelopment of a sac from the stump of the cystic duct. The dilatation often assumes the shape of a miniature gall bladder, although it is somewhat more clubbed and much smaller. Histological sections through the involved areas have the appearance of those from an ordinarily diseased gall bladder.[2]

After cholecystectomy, there is a general enlargement of all the bile ducts, as was observed by Oddi in his experimental work. This continues for a time until there is complete relaxation of the sphincter of Oddi, thus permitting the bile to flow continuously into the duodenum.

The stump of the cystic duct participates in the general enlargement and dilatation of all ducts.[3] Thus, there is a dilated cystic duct with a secreting mucous membrane acting as a receptacle for bile, but lacking the contractile ability of a normal gall bladder. Any obstruction at the junction of the dilated remnant of the cystic duct and common duct, the secreted mucoid material with bile accumulating behind the obstruction, may be sufficient to initiate the re-formation of a "gall-bladder"-like structure. In time, the presence of mucoid material and stagnant bile in the pouch-like stump of the cystic duct may be followed by infection, inflammation, and, at times, the formation of stones.

The process may also be initiated by cystic duct calculi which are missed by palpation and probing during the original operative procedure because of the tortuosity of the duct and the presence of the spiral valves of Heister.[4] Because of the almost uniform inflammatory involvement of the cystic duct,[5] other potential hazards may be set up by the long residual duct. As edema and inflammation subside, the free end of the duct may become adherent to the serosal surface of the liver, duodenum, or colon. With cicatricial shortening, traction can distort the normal contour of the common duct, leading to a kinking obstruction.[4]

No definitive symptom complex can be ascribed to the development of a "re-formed gall bladder." In the majority of cases the symptoms are often represent-

1. Beye, H. L.: Conditions Necessitating Surgery Following Cholecystectomy: An Analysis of 66 Cases and a Discussion of Certain Technical Problems Concerned in Removal of the Gall Bladder and in Operation upon the Common Bile Duct, Surg., Gynec. & Obst. **62**:191-202, 1936.

2. Peterson, F. R.: Re-Formed Gall Bladder: Review of 42 Cases, J. Iowa M. Soc. **36**:134-138, 1946.

3. Miller, G. H.: "Re-Formed Gall Bladder," M. Times **76**:302-304, 1948.

4. Hicken, N. F.; White, L. B., and Coray, Q. B.: Incomplete Removal of Cystic Duct as a Factor in Producing Post-Cholecystectomy Complications, Surgery **21**:309-320, 1947.

5. Gray, H. K., and Sharpe, W. S.: Biliary Dyskinesia: The Role Played by a Remnant of the Cystic Duct, Proc. Staff Meet., Mayo Clin. **19**:164-168, 1944.

ative of those complaints which existed prior to the surgical procedure.[1] In the recorded cases the interval between cholecystectomy and onset of signs and symptoms was highly variable. In very few, if any, was it longer than the 17-year interval in this case.

Postoperatively, the commoner disturbances of the bilary tree, such as injury to the major ducts, angulation of the common duct following adhesions, and common duct stones, must be adequately considered and ruled out in differential diagnosis. Failure to visualize the "re-formed gall bladder" with roentgenograms does not permit one to rule out its presence. It can be identified definitely only by reoperation and careful dissection of all ducts. At times, cholangiograms taken while the patient is on the operating table may be of great value.[6] Prophylactically, the surgeon, when performing cholecystectomies, should make every effort possible to ligate the cystic duct close to its junction with the common duct.

SUMMARY

A case of "re-formed gall bladder" with stones following a cholecystectomy 17 years ago is presented. The underlying pathological physiology is discussed. Great care should be exercised at the time of cholecystectomy to remove the entire cystic duct.[7]

417 Ocean Ave. (26).

6. Weingarten, M.: Calculi in a Dilated Stump of the Cystic Duct: Preoperative Visualization, J. A. M. A. **145**:157-159 (Jan. 20) 1951.

7. Morton, C. B., II: Post-Cholecystectomy Symptoms Due to Cystic Duct Remnant, Surgery **24**:779-786, 1948.

JAUNDICE DUE TO LEAD POISONING

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LEAD poisoning as a cause of jaundice is seldom mentioned in the literature. The following case seems worthy of presentation because of this infrequent mention and the unusually severe exposure incurred outside the usual hazardous industries.

REPORT OF CASE

B. B., a 24-year-old white man, was admitted to the hospital Aug. 19, 1950, because of severe abdominal cramping. His health prior to the present illness had been good except for hay fever and asthma during the ragweed and grass seasons for several years. There had been no previous gastrointestinal symptoms. The illness had begun two weeks before with loss of appetite the day he began painting the outside of his house. During the ensuing week, while continuing the work, he suffered from intermittent epigastric cramping, nausea, vomiting, and constipation. Bed rest and the usual home medications did not relieve the discomfort, and the cramping became so severe that he decided to come to the hospital.

Results of physical examination were normal except for slight yellow tinting of the sclerae and marked pallor of the face. The abdomen was soft to palpation and not particularly tender. At this time the possibilities considered included liver or gall-bladder disease, duodenal ulcer, intestinal obstruction, acute pancreatitis, renal colic, and lead poisoning. Results of urinalysis, including a test for bile, were normal. The erythrocyte count was 3,890,000, with 12.2 gm. of hemoglobin per 100 cc., and the hematocrit reading was 38%. No stippling was noted on the blood smear. The leucocyte count was 11,200, with a normal differential count. The erythrocyte sedimentation rate was 25 mm. in 45 minutes (Westergren), representing a moderate elevation. Serum bilirubin was 0.65 mg. on the direct test, with a total of 3.5 mg. Serum amylase was normal. A roentgenogram of the abdomen showed marked gaseous distention of the terminal portion of the small bowel and the proximal two-thirds of the colon, but was otherwise normal. During the next 48 hours, with administration of fluids intravenously and meperidine (demerol®), the abdominal cramping subsided. Roentgenograms of the chest, gall bladder, esophagus, stomach, duodenum, and colon were made but were found to show no pathological changes. The reaction to the cephalin-cholesterol-flocculation test was 1+, which was not considered significant. The test for red cell fragility with hypotonic saline solution gave a normal result.

By Aug. 28, nine days after admission, the jaundice had subsided, and the serum bilirubin was 0.2 mg. on direct test, with 0.95 mg. total. A sulfobromophthalein (bromsulphalein®) sodium test showed no dye retention. The erythrocyte count had fallen to 3,410,000 and the hemoglobin concentration to 10.75 gm.; therefore, iron therapy was instituted. To this point, although lead poisoning had been repeatedly considered, it seemed unlikely, since neither his job as an automobile-parts clerk nor the outdoor painting offered adequate exposure. However, on Sept. 5 a recheck blood smear showed numerous stippled red cells, and the patient was questioned in detail concerning his activity prior to the illness. It was then learned that he had spent three to four hours of spare time daily for five weeks removing the old paint from his entire house with an electric hand sander, using no protective mask! He admitted that he had not considered this work as involving exposure to lead. Necessary equipment was obtained from Dr. R. A. Kehoe, of the Kettering Institute, Cincinnati, and urine and blood samples were submitted to him for lead analysis on Sept. 11, about five weeks after the patient had finished the sanding job. The urine was found to contain 0.075 mg. of lead per liter and the blood 0.08 mg. of lead per 100 gm. Dr. Kehoe [1] commented that "the value of 0.075 mg. of lead per liter (of urine) is within the

1. Kehoe, R. A.: Personal communication to the author.

normal range. However, the results of the blood studies indicate the likelihood of potentially hazardous exposure to lead within recent months, capable of causing illness."

By this time the patient felt well enough to leave the hospital and was discharged Sept. 16. On a recheck two weeks later, many stippled cells were still seen and the urine yielded 0.24 mg. of lead per liter. By Oct. 21 the erythrocyte count had risen to 4,110,000, with 12.2 gm. of hemoglobin, and stippled cells were rare. A blood sample showed 0.05 mg. of lead per 100 gm., which Dr. Kehoe [1] pointed out is "at the extreme upper limit of normal values. The lower level at this time as compared with results reported earlier is to be expected on the assumption that this man has had no occupational exposure to lead in the interim."

COMMENT

The diagnosis of lead poisoning rests on a history of adequate exposure, symptoms compatible with the condition, positive laboratory findings, and exclusion of other causes for the illness.[2] It is beyond the purpose of this discussion to go into detail concerning these points. It suffices to say that the present case seems to satisfy all these requirements and to justify the conclusion that lead poisoning was satisfactorily demonstrated to be the cause of the illness.

The literature makes little mention of jaundice in lead poisoning. Jones [3] listed it as suggestive evidence of more advanced plumbism and noted that in his cases it occurred with about the same frequency as pallor. Kehoe and associates [4] stated that jaundice is rare and occurs only in neglected or far-advanced cases with extensive blood destruction. This is not inconsistent with the present case, since it is generally agreed that inhalation of lead dust comprises the most dangerous type of exposure,[5] and Cotter [6] stated that in the inhalation type of poisoning the symptoms are so acute that the worker is forced to quit work relatively early in the course of the illness.

The jaundice of plumbism is apparently hemolytic, rather than hepatic. Goodman and Gilman [7] pointed out that it is probably the result of increased destruction of red blood cells, since there are no pathological changes found in the liver to account for it. In the case under discussion the normal gall-bladder roentgenogram, cephalin-cholesterol flocculation, and sulfobromophthalein excretion on the one hand, and the acholuria, anemia, and elevated indirect van den Bergh reaction on the other, all point to a hemolytic process. The phenomenon of stippling may also be

2. Kehoe, R. A.: Lead Absorption and Lead Poisoning, M. Clin. North America **26**:1261-1279 (July) 1942.

3. Jones, R. R.: Symptoms in Early Stages of Industrial Plumbism, J. A. M. A. **104**:195-200 (Jan. 19) 1935.

4. Kehoe, R. A.; Aub, J.; Belknap, E.; Dreessen, W. C.; Gehrmann, G. H.; Kronenberg, M. H.; Mayers, M. R., and Yant, W.: Occupational Lead Exposure and Lead Poisoning: Report Prepared by Committee on Lead Poisoning of the Industrial Hygiene Section of the American Public Health Association, New York, American Public Health Association, 1943.

5. Kehoe and others.[4] Brown, E. W.: Health Hazards from Lead Paint and Zinc Chromate Paint, Occup. Med. **5**:739-758 (June) 1948. Wormser, F. E.: Facts and Fallacies Concerning Exposure to Lead, ibid. **3**:135-144 (Feb.) 1947.

6. Cotter, L. H.: Lead Intoxication by Inhalation, J. Indust. Hyg. & Toxicol. **28**:44-46 (March) 1946.

7. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, The Macmillan Company, 1941, p. 727.

regarded as indirect evidence of blood destruction. Sanders [8] emphasized that stippling is by no means limited to lead poisoning, and Pearlman and Limarzi [9] observed that it occurs whenever there is any cause for an erythroid response, such as the anemias of terminal nephritis, thrombocytopenic purpura, leukemia, pernicious anemia under liver therapy, and lead poisoning. Their observations suggested that stippled cells and reticulocytes are identical. In this regard, blood studies for stippling in a case of untreated pernicious anemia with concomitant plumbism would be of utmost interest.

The actual mechanism of the hemolysis is not clear. The red cell fragility as measured by hypotonic saline solution was normal. Aub and co-authors [10] in their investigations noted this paradox and offered a possible explanation for it. They suggested that the lead reacts with the lipid-protein film which constitutes the red cell membrane, causing it to shrink and become less elastic. These changes render the cells more resistant to the osmotic tension of hypotonic saline solution but, at the same time, make them more fragile and less resistant to the trauma of circulation. They concluded that there is an interrelationship of stippling, anemia, and changes in resistance to hypotonic saline solution, since all three features were present in cells from certain species and all absent in others.

SUMMARY

A report of a case of jaundice due to lead poisoning is presented. The jaundice was apparently hemolytic, probably resulting from increased friability of the erythrocytes, caused by the direct action of lead on the cell surfaces.

The intoxication was incurred outside the usual hazardous industries, yet involved prolonged severe exposure to lead in its most dangerous form. With the increasing tendency for the home handy man to attempt all kinds of repair jobs without knowledge of adequate protection, such cases are likely to become more frequent.

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8. Sanders, L. W.: Measurement of Industrial Lead Exposure by Determination of Stippling of the Erythrocytes, J. Indust. Hyg. & Toxicol. **25**:38-46 (Feb.) 1943.

9. Pearlman, M. D., and Limarzi, L. R.: Correlation Studies of Basophilic Aggregation and Reticulocytes in Various Clinical Conditions, Am. J. Clin. Path. **8**:608-619 (Nov.) 1938.

10. Aub, J. C.; Fairhall, L. T.; Minot, A. S., and Reznikoff, P.: Lead Poisoning, Medicine **4**:1-250 (Feb.-May) 1925.

Progress in Internal Medicine

STUDIES IN MITRAL STENOSIS

III. The Effect of Ouabain on the Circulation in Patients with Pulmonary Disability

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DIGITALIS substances are usually employed in the treatment of patients with mitral stenosis who display clinical symptoms of either marked dyspnea or peripheral congestion. The clinical responses of these patients to such therapy may be gratifying, but not infrequently the drugs appear to exert no beneficial effect and may even be deleterious. The reasons for such varying responses to this therapeutic measure are poorly understood by most clinicians, who are likely to employ broad generalizations in their attitudes regarding the use of digitalis in mitral stenosis, varying from never giving it to giving it routinely in all cases. The variable response to the drug in mitral stenosis can be understood better on consideration of the fact that the disabilities resulting from rheumatic heart disease with mitral stenosis vary greatly in their physiologic and anatomic nature. The fundamental lesion in mitral stenosis is a narrowing of the mitral orifice, resulting in increase in pressure in the circulation behind it, namely, in the left auricle and throughout the pulmonary blood vessels. It is this pulmonary hypertension that is fundamentally responsible for the dyspnea which is usually the earliest and chief symptom; in most patients with mitral stenosis such dyspnea is aggravated by any condition which interferes with a sufficient flow of blood through the mitral orifice or which tends to increase the output of the right ventricle with respect to the runoff through the mitral orifice.[1] Among such conditions, tachycardia, either in patients with normal rhythm or especially in those with auricular fibrillation, is important. In addition, right-sided heart failure may occur as a result of the chronic strain of pulmonary hypertension, because of active or preceding myocarditis, or from strain due to aortic valvular disease. If digitalis is effective in slowing the heart rate and thus improving

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1. Ellis, L. B.; Bloomfield, R. A.; Graham, G. K.; Greenberg, D. J.; Hultgren, H. N.; Kraus, H.; Maresh, G.; Mebane, J. G.; Pfeiffer, P. H.; Selverstone, L. A., and Taylor, J. A.: Studies in Mitral Stenosis: I. A Correlation of Physiologic and Clinical Findings, A. M. A. Arch. Int. Med. **88**:515 (Oct.) 1951.

the flow through the mitral valve, then its use may be beneficial; if, however, it acts to increase the output of the right ventricle at a time that the flow through the mitral valve of the left side of the circulation cannot be increased, it may serve merely to accentuate the disparity between the effectiveness of the two sides of the heart and to increase pulmonary congestion, even though peripheral congestion may occasionally be somewhat decreased. Under such conditions the clinical results may be far from useful.

In the course of a general study of the hemodynamics of heart failure,[2] it became apparent that the data obtained from patients with mitral stenosis were different from those obtained from patients with heart disease of other anatomic and etiological backgrounds. Accordingly, the findings in a small group of patients with mitral stenosis who were given the quick-acting cardiac glycoside ouabain will be presented in some detail.

In a previous report [2] from this laboratory, subsequently confirmed by Ahmed and associates,[3] it was pointed out that patients suffering from right- and left-sided heart failure due to the degenerative (hypertensive and arteriosclerotic) types of heart disease and to aortic valve disease show a fairly uniform type of response to the administration of ouabain. By the time the first observations are made, 10 to 60 minutes after injection of the drug, there is usually a prompt and demonstrable increase in the initially subnormal cardiac output. Frequently, but not invariably, and to a varying degree, there is a decline in the peripheral venous pressure and right auricular and ventricular diastolic pressures. The pulmonary arterial and right ventricular pulse pressures may show a rise. The systemic arterial pulse pressure usually increases. The heart rate may decline, particularly when auricular fibrillation with a rapid ventricular beat occurs, but does not do so in every case. The stroke volume of the heart beat increases. We concluded that the primary effect of ouabain upon the heart in these cases is to increase its contractility by a direct action on the ventricular myocardium.

Ahmed, Bayliss, Briscoe, and McMichael [3] have shown that when ouabain is administered to patients with normal circulation there is no significant effect on the cardiac output or the right auricular pressure. There may or may not be a slight early hypertensive effect on the peripheral arterial pressure, which is usually not sustained, and slight slowing of the heart beat.

PRESENT STUDY

The present report is concerned with the study on five patients with high-grade mitral stenosis, but without other evidence of heart disease, who suffered in varying degrees from symptoms of pulmonary disability but who had never had any clinical evidence of right-sided failure as manifested by peripheral congestion. (Patient 1 was reported on as Patient 9 in our previous communication.[2]) A brief clinical description of these patients follows:

PATIENT 1.—This patient was a 48-year-old longshoreman who was able to carry on his work at the time these studies were made. The only complaint that he admitted to was cough,

2. Bloomfield, R. A.; Rapoport, B.; Milnor, J. P.; Long, W. K.; Mebane, J. G., and Ellis, L. B.: The Effects of the Cardiac Glycosides upon the Dynamics of the Circulation in Congestive Heart Failure: I. Ouabain, J. Clin. Invest. **27**:588 (Sept.) 1948.

3. Ahmed, S.; Bayliss, R. I. S.; Briscoe, W. A., and McMichael, J.: The Action of Ouabain (G-Strophanthin) on the Circulation in Man, and a Comparison with Digoxin, Clin. Sc. **9**:1 (Feb.) 1950.

although he apparently was very mildly dyspneic. On physical examination he had a Grade 3 mitral diastolic and presystolic murmur at the apex but no systolic murmur. The mitral first sound and pulmonic second sound were increased. The lungs were clear, and there was no edema. The heart showed some enlargement of the region of the left auricle and right ventricle by roentgenogram, as well as by electrocardiogram.

PATIENT 2.—A 26-year-old machinist had had known rheumatic heart disease following rheumatic fever since the age of 7 years. He first began to have some shortness of breath at the age of 19, which increased, particularly in the past year, so that he was able to carry on a sedentary occupation only. In addition, he had frequent severe attacks of acute pulmonary edema often accompanied with excruciating, compressing chest pain, and on occasion he had moderate hemoptysis precipitated by excitement or exertion. His clinical course has been unusual, and he has been carefully followed over a period of years, undergoing five cardiac catheterizations of which this was the first. Subsequent to this study, in 1948, an artificial interatrial septal defect had been created in the hope of alleviating his symptoms, with benefit for about three months; in 1950 a mitral valvuloplasty was performed by Dr. Dwight Harken, subsequent to which the patient's condition has been greatly improved. During the months prior to the mitral valvuloplasty, but about three years after these studies were made, he went into progressive right-sided heart failure and was bedridden with congestive failure. At the time these studies were made, however, he had no peripheral congestion but did have moderate chronic dyspnea on exertion, with the acute pulmonary episodes described. (He was reported on briefly as Patient 35 in another communication.[1]) On physical examination he showed a Grade 3 mitral diastolic murmur at the apex. The mitral first sound and pulmonic second were markedly increased. His heart was considerably enlarged in the region of the right ventricle and especially in the left auricle, as seen on teleroentgenographic as well as on electrocardiographic study. There was no edema or enlargement of the liver.

PATIENT 3.—A 29-year-old unmarried woman had had 17 admissions to the hospital, mostly for attacks of hemoptysis. She had known of her heart disease for 12 years. For about 10 years she had had moderate orthopnea and increasing dyspnea on exertion, so that at the time of this study she was unable to climb a flight of stairs without difficulty. On occasion she had had attacks of acute dyspnea, but this did not develop into frank pulmonary edema. She had had many attacks of severe hemoptysis. She had never had peripheral edema or evidence of congestive failure. Physical examination revealed an extremely thin, underdeveloped young woman. Her heart was slightly enlarged in the region of the right ventricle and the left auricle clinically and on teleroentgenogram and electrocardiogram. A Grade 3 diastolic and presystolic murmur at the apex but no systolic murmur and a Grade 1 early blowing diastolic murmur along the left border of the sternum were noted. The mitral first sound and pulmonic second sound were markedly increased. There was no enlargement of the liver and no peripheral congestion.

PATIENT 4.—A 58-year-old housewife had known of her heart disease for the past 19 years. For years she had had mild dyspnea on exertion; however, this had not markedly interfered with her activity and was not progressive. Otherwise, her symptoms were unremarkable. She was operated on without event in July, 1947, for an obstructing gastric ulcer, and a subtotal gastric resection was performed. Cardiac studies were made on Oct. 30 of the same year. On physical examination, her heart was considerably enlarged in the region of the right ventricle and left auricle clinically and on teleroentgenogram and electrocardiogram. A Grade 2 mitral diastolic murmur and a Grade 1 apical systolic murmur were detected. The pulmonic second and mitral first sound were increased. There was no enlargement of the liver or evidence of peripheral congestion.

PATIENT 5.—A 42-year-old steeplejack had had increasing dyspnea over the past nine years. At the time of the studies he was unable to walk on the level without becoming markedly dyspneic, and he became dyspneic at rest when excited. There was little or no orthopnea. He had moderate cough and palpitation; he had had several attacks of production of blood-streaked sputum, and on one or two occasions severe hemoptysis had occurred. In spite of these he had worked at his profession, although he had been unable to carry on more than a supervisory type of work for some time. His heart was markedly enlarged. There was a Grade 3 diastolic murmur at the apex but no systolic murmur. The mitral first sound and the pulmonic second sound were increased. Along the left border of the sternum there was a Grade 1 early diastolic

blowing murmur. The lungs were clear. The liver was not enlarged, and there was no peripheral congestion. By fluoroscopy and electrocardiogram the right ventricle and left auricle were enlarged, and there was probable enlargement of the left ventricle as well.

It is evident that three of these patients (*2*, *3*, and 5) were seriously disabled by their disease, and in many ways their clinical condition was equivalent to that of patients with congestive failure of other types. They are the type of patient who would ordinarily be given digitalis clinically, as would Patient 4 with auricular fibrillation.

The procedure employed in this study was the same as that described previously.[2] The zero point of reference of the intracardiac and peripheral venous pressures was taken as 5 cm. below the angle of Louis.

The ouabain was administered in doses of 0.4 to 0.6 mg. Patient 1 received 0.5 mg.; Patient 2 was given 0.63 mg., and Patients 3, 4, and 5 received 0.4 mg.

RESULTS

It is apparent from the table that the pattern of response to ouabain was highly variable. Of three patients with normal sinus rhythm, two showed a drop in cardiac

Response to Ouabain in Patients with Pulmonary Disability

Patient No.		Cardiac Output, L./Min.	Cardiac Index, L./Min./Sq. M.	Heart Rate/Min.	and Rhythm	Stroke Volume, Cc.	Pulmonary Arterial Pressure, Mm.Hg			Right Ventricular Pressure, Mm.Hg			Femoral Artery Pressure, Mm.Hg		
							Systolic	Diastolic	Mean	Systolic	Diastolic	Venous Pressure, Mm.Hg	Systolic	Diastolic	Mean
1	Control	5.1	2.9	85	Sinus	60	..	..	..	44	11	..	111	66	78
	128 min.	4.4	2.5	84	arrhythmia	52	..	..	..	43	4	..	122	74	93
2	Control	7.0	3.7	82	Normal	85	39	21	29	35	2	2	93	58	75
	15 min.	7.6	4.1	64	sinus	121	33	25	29	33	4	8	102	63	79
	70 min.	4.5	2.4	55		81	53	29	40	55	8	7	107	63	78
3	Control	3.5	2.8	75	Normal	47	89	42	..	90	8	8	125	67	..
	10 min.	3.8	3.0	94	sinus	40	90	43	..	87	6	7	121	65	..
	62 min.	4.1	3.2	79		51	79	44	..	70	3	5	133	69	..
4	Control	3.4	1.9	148	Auricular	23	..	..	..	62	10	10	103	82	88
	10 min.	4.0	2.2	128	fibrillation	31	..	..	..	62	9	7	117	88	99
	60 min.	3.7	2.0	124		30	..	..	..	52	9	6	113	85	94
5	Control	3.9	2.7	96	Auricular	41	41	28	31	40	..	9	115	77	99
	25 min.	4.0	2.8	73	fibrillation	55	44	24	27	41	..	8	136	72	92
	58 min.	4.1	2.9	64		64	45	28	32	50	..	7	150	91	109

output by the end of their observation period. In Patient 1 the decline in output was wholly attributable to a diminution of the individual stroke volume with no change in heart rate. The right ventricular systolic pressure remained unchanged, while the diastolic (filling) pressure fell from 11 to 4. There was an accompanying rise in the systemic arterial pressure, systolic, diastolic, and mean. The fall in output in the presence of a rising mean arterial pressure thus indicates an increase in the peripheral vascular resistance. Two explanations for these results are suggested. It may be that the chief effect of ouabain in this patient was to bring about peripheral arteriolar constriction with consequent diminution in the arteriolar runoff, leading in turn to a lessened venous return, lowered ventricular filling pressure, and hence a smaller stroke output. The peripheral arterioles are not, however, regarded as the main site of action of ouabain, although a transitory hypertensive effect of this drug has been described.[3] An alternative explanation of this finding is that the chief action of the drug was to decrease still further the initially

normal diastolic size of the left ventricle, whereby the volume intake during diastole was decreased. In this case the rise in peripheral resistance could be regarded as a compensatory response to the diminished arterial filling, with a resultant fall in venous return and in right ventricular filling pressure.

In Patient 2 the cardiac output was found to have risen at the end of 15 minutes after ouabain administration, but at the end of 70 minutes it showed a marked decline. The heart rate fell from 82 to 55; pulmonary arterial and right ventricular and peripheral venous pressures rose. There was only a very slight rise in the mean pressure in the femoral artery. The unique feature about this patient at the time this study was carried out, as well as in a cardiac catheterization done six months following this one, was his ability to develop a normal or even elevated cardiac output at rest or on excitement or exercise. In our experience,[1] patients subject to attacks of acute pulmonary edema frequently have normal cardiac outputs at rest and not infrequently can increase them on exertion. This may be true even in the presence, as demonstrated at operation or at postmortem study, of marked stenosis of the mitral valve. Almost all these patients are in normal sinus rhythm, and it is possible that auricular contraction may contribute to an ability to maintain an adequate cardiac output. An alternative explanation would be that their cardiac musculature is still completely adequate and the force of right ventricular ejection is well maintained. In addition, as suggested by Gorlin and co-workers,[5] these patients apparently lack the factor of unusual increase in precapillary resistance in the pulmonary circulation which serves as a protective mechanism preventing unusual increment of pressure from reaching the pulmonary capillaries in the venous system.

In the present study, the initial increase in cardiac output and especially in stroke volume was accomplished without rise in either pulmonary arterial or peripheral arterial pressures and appears to have been a function of a decrease in cardiac rate permitting improvement in flow through the mitral orifice during the longer diastolic period. At the end of 70 minutes, however, there was a decrease in cardiac output per minute and per beat at the time that the heart rate further decreased. At this time pulmonary arterial, right ventricular diastolic, and peripheral venous pressures had increased. The probable explanation of this is that the early increase of cardiac output had resulted in the gradual development of pulmonary congestion with an accumulation of blood in the pulmonary circulation because of the barrier of the stenosed mitral orifice. When this had reached a certain point, the pulmonary hypertension with its increased strain on the right ventricle caused physiologic failure of the right ventricle with a decrease in output. At this time the blood reaching the heart from the peripheral venous circulation could not be adequately handled, and congestion in the peripheral circulation developed. Thus, a balance was established, but only by the creation of what virtually was heart failure. In Patient 2, therefore, digitalis could be said to have a definitely deleterious effect.

In Patient 3, with normal sinus rhythm, there was a moderate rise in the cardiac output which appeared to be due at first to an increase in heart rate, and it is of

4. Footnote deleted.

5. Gorlin, R.; Sawyer, C. G.; Haynes, F. W.; Goodale, W. T., and Dexter, L.: Effects of Exercise on Circulatory Dynamics in Mitral Stenosis, Am. Heart J. **41**:192 (Feb.) 1951. Gorlin, R.; Lewis, B. M.; Haynes, F. W.; Spiegel, R. J., and Dexter, L.: Factors Regulating Pulmonary "Capillary" Pressure in Mitral Stenosis, ibid. **41**:834 (June) 1951.

interest that at this time the stroke volume had actually decreased. The finding at the end of 62 minutes, when the rise in output had continued, coincided with a fall in heart rate to approximately that of the control. At this time the stroke volume had improved and was now slightly greater than the control output per beat. The final change in the pulmonary arterial pressure was a decrease, which suggests a slight decrease in pulmonary congestion.

The two patients with auricular fibrillation both showed marked decreases in heart rate after receiving ouabain.

There was a very slight rise in the output in Patient 4, but so small as to be a doubtful result of the drug. There was no significant change in the right ventricular, pulmonary arterial, or peripheral venous pressure, but a definite increase took place in the systemic arterial pressure.

Patient 5 showed a modest rise in cardiac output with some increase in stroke volume which can be accounted for by the considerable decrease in heart rate. Changes in right ventricular and femoral artery pressures were probably within the range of normal variation, although the slight tendency for a decrease in right ventricular pressure suggested some decrease in pulmonary congestion. Lowering of the peripheral venous pressure was probably of significance and was consistent with a better emptying of the right ventricle.

In each of the last two patients there was a definite increase in the individual stroke volume. The latter increase cannot be attributed to a direct effect of the drug upon the ability of the myocardium to increase its output, since with the lessened heart rate the longer diastolic filling interval between beats permitted a greater stroke output. What increase was observed in the cardiac output may well have been caused by the correction of some element of myocardial failure due to the presence of auricular fibrillation with a heart rate that was more rapid than optimal for those patients.

COMMENT

While the results in these five instances showed a variable and unpredictable response to the giving of ouabain, the patients all had in common a lack of ability to increase their cardiac output primarily by a significant increase in the individual stroke output for a given diastolic filling time. Three patients did increase their cardiac outputs and stroke volumes, although in one (Patient 2) this was a transitory phenomenon. In this patient the increase in stroke volume was accompanied with considerable decrease in heart rate; but apparently it was a deleterious effect, since later findings suggested the development of congestive failure. In the last two patients (4 and 5) the augmentation of the stroke volume appeared to be definitely related to a decrease in heart rate, although in one of these (Patient 4) there was no change in the minute volume output of the heart. Patient 3 showed a slight increase in cardiac minute output which ultimately was effected by a slightly greater stroke output plus a slight increase in rate. This inability to improve the output of the heart for a given diastolic interval when ouabain is administered is thought to be due to the limiting factor of a stenosed mitral orifice, as contrasted with the circumstances in patients with other types of heart disease who have equivalent degrees of pulmonary symptoms, but in whom myocardial weakness is the greatest factor.

The findings as reported in the present communication do not necessarily apply to patients with mitral stenosis who are in severe congestive failure and in whom

actual myocardial failure may be a significant element in the production of their symptoms. In the literature there are a number of reports of the effects of the cardiac glycosides on patients with congestive failure, and patients with mitral stenosis are included in some of these reports, although in many instances these patients had also disease either of the aortic valve or of other origin. In some of these, as, for example, in the patients reported on by Harvey and associates,[6] the mitral stenosis was apparently not important in producing the congestive failure. Ahmed, Bayliss, Briscoe, and McMichael [3] reported the effect of the administration of ouabain to four patients with mitral stenosis, one of whom did not have heart failure. The latter patient showed no change in his cardiac output, although a slight slowing of the pulse rate resulted in an increase in output per beat. Of the three patients with failure, one showed a marked increase in cardiac output with a slight increase in heart rate. The other two showed virtually no change in cardiac output, although one had a decrease in the heart rate. These same authors cited 10 patients with mitral stenosis who were treated with digoxin. Of these 10 patients, 4 had associated aortic disease and 3 had auricular fibrillation. Since the authors did not report the heart rate changes in these patients, it is impossible to determine what factor change in heart rate may have been as an element in improving cardiac output. Of the 10 patients, 9 showed a definite increase in the cardiac output, usually of considerable magnitude. Stead, Warren, and Brannon,[7] in their communication concerning the effect of lanatoside C in congestive failure, included four patients with mitral stenosis. One of these showed a marked increase in cardiac output and stroke volume, associated with marked slowing of the heart rate. Two showed very little change in blood flow, and the third showed a decrease in output and stroke volume with no change in heart rate. For none of these patients are clinical data given which indicate whether the patient cited suffered from generalized congestive manifestations.

In another communication [1] we have pointed out that patients with mitral stenosis, even if high grade, frequently have cardiac outputs per minute at rest which are within the normal range and that low outputs are more commonly found in patients who have generalized congestion, suggesting perhaps that in the latter patients myocardial failure has occurred. In the present study only one patient (5) had a control cardiac output that was clearly reduced before ouabain administration. In this patient the heart rate was very rapid, which was certainly a factor, in the presence of mitral stenosis, in the production of such a low output. In the discussion of Ahmed and associates on ouabain, their two patients who clearly had low cardiac outputs both showed increases after therapy, whereas two patients with either a borderline or a normal cardiac output showed no change. None of their patients who had been given digoxin had a normal control output, although one was of perhaps borderline significance. In the patients reported on by Stead and colleagues,[7] two had clearly low control cardiac outputs, and, of these, one showed a marked increase in both minute and stroke output. The other showed a slight increase in

6. Harvey, R. M.; Ferrer, M. I.; Cathcart, R. T.; Richards, D. W., Jr., and Cournand, A.: Some Effects of Digoxin upon the Heart and Circulation in Man: Digoxin in Left Ventricular Failure, Am. J. Med. **7**:439 (Oct.) 1949.

7. Stead, E. A., Jr.; Warren, J. V., and Brannon, E. S.: Effect of Lanatoside C on the Circulation of Patients with Congestive Failure: A Study Using Catheterization of the Right Side of the Heart, Arch. Int. Med. **81**:282 (March) 1948.

minute output but a questionable increase in the stroke-volume output. Of the two patients whose outputs were probably within the normal range, one showed a slight increase in the output but no change in the stroke output, and the other showed a decrease. Thus, there may be some effect of the cardiac glycosides in increasing the output in patients with mitral stenosis when actual myocardial weakness is a factor.

This study shows the inadvisability of including patients with mitral stenosis in any general group with heart disease when considering the hemodynamic effects of therapeutic agents or other measures on the circulation, since mitral stenosis is unique in that it presents a mechanical barrier to the circulation which certainly modifies the results.

As can be seen from the foregoing study, there is no consistent response to the cardiac glycosides in patients with mitral stenosis. In some, particularly those with tachycardia usually accompanying auricular fibrillation, and in many with generalized congestion, the glycosides may be of benefit. Others, however, may receive no benefit from the drug, or it actually may have a deleterious effect.

SUMMARY AND CONCLUSIONS

A study is reported of the hemodynamic effects in the administration of ouabain intravenously to five patients with mitral stenosis. None of these patients had clinical right-sided heart failure or had had a history of congestive failure. They suffered from varying degrees of chronic dyspnea, and three of them were virtually incapacitated. The response to ouabain was variable and unpredictable, but all patients lacked the ability to increase their cardiac output primarily by a significant increase in individual stroke output for a given diastolic filling time. This is believed to be due to the limiting factor of the stenosed mitral orifice. The clinical implications of this study are discussed.

CANICOLA FEVER

Report of Nine Cases in One Family, with Abstract of the World Literature

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LEPTOSPIRAL infections are endemic throughout the world. Weil's disease (leptospirosis icterohemorrhagiae), the commoner and severer of the two principal forms, has been widely discussed in the literature since its first description in 1886.[1] Canicola fever (leptospirosis canicola), on the other hand, is sparsely reported on, perhaps because of its more recent clinical recognition (1937),[2] its relatively benign course, and its comparative rarity. In the light of these facts, the present report of nine cases of the latter disease occurring in one family would appear to be especially significant.

This report was initially prepared with a complete review of the world literature on canicola fever, but with the current appearance of Rosenberg's [3] exhaustive and commendable review it was decided necessary to abstract only the more significant contributions to the problem.

CAUSATION AND INCIDENCE

The causative organisms of leptospiral infections are morphologically identical even under the electron microscope.[4] The spirochetes are delicate, motile, tightly coiled, corkscrew-shaped organisms, with a hook usually on one end, and measure about 0.25 by 10 to 15 μ. Clinical distinction between Leptospira icterohemorrhagiae and Leptospira canicola rests primarily on the agglutination-lysis test of Schüffner and Mochtar or one of its modifications.[5]

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1. Weil, H. A.: Ueber eine eigenthümliche, mit Milztumor, Icterus und Nephritis einhergehende, acute Infectionskrankheit, Deutsches Arch. klin. Med. **39**:209-232, 1886.

2. Roos, C. J.; Walch-Sorgdrager, B., and Schüffner, W. A. P.: Een epidemie van L. canicola-infectie bij menschen en honden, Nederl. tijdschr. geneesk. **81**:3324-3335, 1937.

3. Rosenberg, B. L.: Canicola Fever: Review, with Report of 2 New Cases, Am. J. Med. **11**:75-91, 1951.

4. Morton, H. E., and Anderson, T. F.: Morphology of Leptospira Icterohemorrhagiae and L. Canicola as Revealed by the Electron Microscope, J. Bact. **45**:143-146, 1943.

5. (*a*) Schüffner, W. A. P., and Mochtar, A.: Versuche zur Aufteilung von Leptospirenstämmen, mit einleitenden Bemerkungen über den Verlauf von Agglutination und Lysis, Zentralbl. Bakt. **101**:405-413, 1927. (*b*) Gardner, A. D.: Agglutination of Leptospirae, Lancet **1**:20-21, 1947. (*c*) Raven, C.: Canine Leptospirosis in Pennsylvania, J. Infect. Dis. **69**:131-137, 1941.

From the standpoint of likely unreported and unrecognized cases, the incidence of canicola fever doubtless exceeds that which reported cases would imply. In the United States only 16 cases have been recorded in the literature to date,[6] representing a disproportionately low incidence when compared with the total of 114 cases reported from Switzerland,[7] Denmark,[8] and the Netherlands,[9] whose aggregate population is roughly one-eighth that of this country. No conclusive evidence exists to indicate that the disease should be more prevalent in these foreign countries, except that the incidence of leptospirosis was much higher among persons who fell accidentally into the Amsterdam canals.[10] Minkenhof's 17 cases appear to be the largest single series reported to date.[7c] Two hundred thirteen case reports have thus far accumulated in the world literature, 49 of which are from the Netherlands. It seems reasonable that the preponderance of cases in the latter area is in large measure due to keener awareness of the disease and careful case finding by

6. (*a*) Rosenberg.[3] (*b*) Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: Epidemiology of Leptospirosis, Am. J. Pub. Health **29**:347-353, 1939. (*c*) Greene, M. R.: A Survey of Leptospirosis in Southern California, Am. J. Hyg. **34**:87-90, 1941. (*d*) Bruno, F. E.; Wilen, C. J. W., and Snavely, J. R.: Spirochetal Jaundice: A Report on 15 Cases, Including 2 Cases of Leptospira Canicola Infection, J. A. M. A. **123**:519-524 (Oct. 30) 1943. (*e*) Tievsky, G., and Schaefer, B. G.: Canicola Fever (Leptospirosis Canicola): Report of a Human Case and Review of the Literature, M. Ann. District of Columbia **13**:11-16, 1944. (*f*) Manchester, B.; Larson, C. L., and Thomas, L. J.: Weil's Disease in the District of Columbia: Report of 4 Cases, ibid. **13**:133-138, 1944. (*g*) Rosenbaum, H. D.: Canicola Fever: Case Report and Review of the Literature, Arch. Int. Med. **78**:531-543 (Nov.) 1946. (*h*) Randall, R.: Canine Leptospirosis, Pennsylvania Univ. Vet. Extension Quart. No. 106, pp. 49-57, 1947. (*i*) Doerner, A. A., and Hernandez, T.: Canicola Fever: A Case Report, Mil. Surgeon **103**:368-371, 1948. (*j*) Molner, J. G.; Meyer, K. F., and Raskin, H. A.: Leptospiral Infections: A Survey, J. A. M. A. **136**:814-819 (March 20) 1948. (*k*) Turrell, R. C., and Hamburger, M.: Canicola Fever with Meningitis: Report of a Case in a Human Treated with Penicillin, Am. J. Med. **10**:249-253, 1951.

7. (*a*) Chapius, J. P., and Jéquier-Doge, E.: Une infection rare à leptospires (type canicola), Schweiz. med. Wchnschr. **76**:279-280, 1946. (*b*) Gsell, O., and Kanter, U.: Canicola-Fieber in der Schweiz, ibid. **75**:713-715, 1945. (*c*) Minkenhof, J. E.: Leptospirosis Canicolaris, Lancet **2**:8-10, 1948.

8. Brammer, E.; Petersen, C. B., and Scheel-Thomsen, A.: Et tilfaelde af den Mb. Weilii naerstaaende leptospirosis canicolaris, Ugesk. læger **100**:419-423, 1938. Petersen, C. B.: Om Weils sygdom og andre i Danmark forekommende leptospiroser, ibid. **106**:617-629, 1944. Bukh, N.: Et tilfaelde af leptospirosis canicolaris med udtalt nephropathi, ibid. **102**:1142-1145, 1940.

9. (*a*) Minkenhof.[7e] (*b*) Roos and others.[2] (*c*) Dhont, C. M.; Klarenbeek, A.; Schüffner, W. A. P., and Voet, J.: De leptospiroses bij den hond en de betekenis der Leptospira canicola, Nederl. tijdschr. geneesk. **78**:5197-5208, 1934. (*d*) Walch-Sorgdrager, B.: Leptospiroses, Bull. Health Organ., League of Nations **8**:143-386, 1939. (*e*) Schüffner, W. A. P.: Recent Work on Leptospirosis, Tr. Roy. Soc. Trop. Med. & Hyg. **28**:7-37, 1943. (*f*) Walch-Sorgdrager, B., and Schüffner, W. A. P.: Die Selbständigkeit der L. canicola, Zentralbl. Bakt. **141**:97-109, 1938. (*g*) Schüffner, W. A. P.; Kotter, G. F., and Schultsz, D.: Ervaringen over menschelijke besmettingen met hondenleptospiren (L. canicola), Geneesk. tijdschr. Nederl.-Indië **75**:534-548, 1935. (*h*) Roos, C. J.: Een op meningitis gelijkend geval van de ziekte van Weil, veroorzaakt door de Leptospira canicola, Nederl. tijdschr. geneesk. **81**:33-36, 1937. (*i*) Schüffner, W. A. P., and Walch-Sorgdrager, B.: Infection humaine par Leptospira canicola: deux nouveaux cas, Bull. Office internat. hyg. pub. **29**:297-306, 1937. (*j*) Minkenhof, J. E.: Febris canicolaris, een zeldzame zoönose? Nederl. tijdschr. geneesk. **91**:1938-1946, 1947.

10. Schüffner, W. A. P., and Walch-Sorgdrager, P.: Meningitis in Course of Weil's Disease, Nederl. tijdschr. geneesk. **80**:3000-3007, 1936.

the Institute of Tropical Hygiene in Amsterdam. Forty-two cases are reported from Germany.[11]

Since the incidence of Lept. canicola in dogs may be at least as high as 38% [7e] (with or without active infection), it is likely that many subclinical cases in human beings escape detection. In canicola fever the sex incidence approaches equality, whereas Weil's disease occurs predominantly in men. It has been said that the disease is commoner in the latter half of the year,[9d] although this statement has been challenged.[6j]

EPIDEMIOLOGIC ASPECTS

An epidemiologic discussion of the several leptospiral infections in man exceeds the premise of this paper, but Table 1 is presented in order that the broad scope of this subject is not lost sight of in discussing one form of leptospirosis.

A fundamental concept of the epidemiology of canicola fever derives principally from knowledge that the disease is exclusively a canine infection transmissible to man only through contact with dog excreta, chiefly the urine. This fact stands in

TABLE 1.—*Some Leptospirae Pathogenic to Man**

Leptospira	Disease in Man	Animal Reservoir	Geographical Distribution
Lept. icterohemorrhagiae	Weil's disease	Rattus norvegicus	World-wide
Lept. grippotyphosa	Swamp fever	Species of mice	Europe, Netherlands East Indies
Lept. sejroe	Swamp fever, infectious jaundice	Rats	Denmark, Italy
Lept. canicola	Canicola fever	Dogs	World-wide
Lept. hebdomadis	Japanese 7-day fever	Mice	Japan
Lept. bataviae	Infectious jaundice	Rats, mice	Netherlands East Indies, Japan, Italy
Lept. pomona	Swineherd's disease	Rats	Australia, Italy, Switzerland

* From Sacks.[21a]

curious contrast to Weil's disease, the animal vectors of which are rats, dogs, mice, cats, pigs, foxes, mongooses, poultry, bandicoots, and horses. Lept. canicola has never been shown to infect naturally any animal but the dog,[6j] yet the latter is a common carrier of Lept. icterohemorrhagiae and several other leptospirae. Specifically, it has never been demonstrated in the rat population.[6b] Indeed, it is a common and serious disease in dogs. It is said that 50 to 90% of dogs over 6 years of age have residuals of latent infection from or positive reactions to Lept. canicola.[12] Roughly, only 50% of cases of human canicola fever are probably directly traceable to infected dogs.

11. Stödter, A.: Ein seltner Fall von Weil-Spirochäteninfektion von Typ Canicola, Berl. tierärztl. Wchnschr. **54**:261, 1938. Günther-Kühne, H.; Rimpau, W., and Schubert, N.: Über 20 Fälle von Canicolafieber, Deutsche med. Wchnschr. **74**:129-133, 1949. Port, F., and Rimpau, W.: Canicola-fieber, Med. Monatsschr. **2**:33-36, 1948. Armbrust, K.: Über einen Fall von Canicolaleptospirose beim Menschen, Deutsche med. Wchnschr. **74**:153, 1949. Mackay-Dick, J., and Watts, R. W. E.: Canicola Fever in Germany: Report of 6 Cases, Lancet **1**:907-910, 1949. Wedekind, P., and Steigner, K. F.: Über Canicolafieber in Hannover, München. med. Wchnschr. **92**:1291-1294, 1950.

12. Rosenbaum.[6g] Babudieri, B., and Castagnoli, B.: Ricerche sulla frequenza dell'infezione de leptospire nei cani di Roma, Ann. d'ig. **50**:145-162, 1940.

The symptoms and pathologic characteristics of canine leptospirosis were first described in 1933.[13] The similarity of the clinical symptoms in the dog to distemper, blacktongue, and various gastrointestinal disturbances has been mentioned.[14] The disease may be acute and, more commonly, subacute or chronic. Excellent clinical descriptions are given by Jones [15] and by Witter.[16] The spirochetes have a selective affinity for renal tubules and are eliminated with the urine not only during the illness but for an indefinite period after recovery. The disease assumes two basic forms of equal prevalence in dogs, namely, the icteric form with hepatic damage and the hemorrhagic-uremic form. The two may occur simultaneously, but the chief pathologic feature of either is renal involvement. A dog so afflicted becomes a constant hazard to other dogs and to persons with whom it comes in contact because of persistent leptospiruria. Recognition and isolation of carriers are thus important. The incidence of the infection among dogs is somewhat higher in rural than in urban areas.[5c]

Human beings are infected when Lept. canicola is brought into contact with mucous membranes or broken skin. (Intact skin is impervious to the organism.) Contaminated ponds, food, and drinking water and playing with infected dogs are common sources of infection. Particularly vulnerable are dog catchers and veterinarians. The organisms are said to thrive and retain their virulence as long as three weeks in stagnant water if the reaction of the water is neutral.[17] However, either moderate alkalinity or acidity is spirocheticidal. In a number of reported cases of leptospirosis there is an antecedent history of bathing in rivers.[18]

There is no known natural human immunity to leptospirosis in general or to canicola fever in particular.[19] The incubation period of canicola fever is not definitely established but is thought to approximate that of Weil's disease, namely, one to two weeks.[6g]

It is, of course, important to remember that a dog may be infected with Lept. icterohemorrhagiae or may be a carrier of this organism and thus transmit Weil's disease to human beings in the presence or absence of infection with Lept. canicola. In view of this, simultaneous transmission of both diseases to a human being would seem entirely possible, and, although no such cases have been described to our knowledge, a dual infection was suggested in the study by Molner and associates.[6j] At least two other types of leptospirosis may be transmitted to human beings by

13. Klarenbeek, A., and Schüffner, W. A. P.: Het voorkomen van een afwijkend leptospirenras en Nederland, Nederl. tijdschr. geneesk. **77**:4571-4572, 1933.

14. Newman, J. P.: Studies of Canine Leptospirosis, Am. J. Vet. Res. **11**:405-411, 1950.

15. Jones, T. C.: The Significance of Canine Leptospirosis in Military Preventive Medicine, Mil. Surgeon **106**:183-186, 1950.

16. Witter, R. E.: Clinical Diagnosis and Treatment of Canine Leptospirosis, Vet. Med. **45**:193-195, 1950.

17. Bertucci, E. A., Jr.: Leptospirosis, Am. J. M. Sc. **209**:86-111, 1945.

18. (*a*) Buzzard, E. M., and Wylie, J. A. H.: Meningitis Leptospirosa, Lancet **2**:417-420, 1947. (*b*) Campbell, A. M. G.; Macrae, J.; Manderson, W. G.; Sumner, K. C., and Broon, J. C.: Canicola Fever in Bristol: Clinical, Bacteriological, and Epidemiological Notes on 6 Human Cases, Brit. M. J. **1**:336-340, 1950.

19. Ashe, W. F.; Pratt-Thomas, A. R., and Kumpe, C. W.: Weil's Disease: A Complete Review of American Literature and an Abstract of the World Literature, Medicine **20**:145-210, 1945.

dogs.[20] Transmission of canicola fever from man to man has never been proved, but there is no apparent reason that it should not be possible. The apparently low incidence of canicola fever in human beings compared with the high incidence of infection and carrier states in dogs has been ascribed to two factors: First, the urine of dogs is usually rather acid in reaction, which tends to be spirocheticidal[6g]; second, man is apparently possessed of a high degree of resistance to the infection.

In summary, the epidemiology of leptospiral infections has been inadequately explored in the United States, the literature being generally confined to discussions of Lept. icterohemorrhagiae and Lept. canicola, in disregard of 16 other species that have been described in other countries.[21] Evidence has been presented to suggest the existence of certain of these other forms in the United States.[22] There is a dearth of laboratory services throughout the nation to execute the all-important bacteriological and immunological procedures necessary for precise identification of the various leptospiral organisms and their incident diseases.

Unlike Weil's disease, the mortality rate in canicola fever is low, there being published reports of only one fatal case in England[23] and of only one undisputed fatal case in the United States[6j]; a third unpublished fatality in Holland was mentioned by Dr. J. C. Broom.[21b] This suggests a mortality rate of 1.5%.

One of the most complete epidemiologic reviews of leptospirosis to date is that of Alston, Joshua, Borg-Petersen, Broom, Stuart, Field, and Edwards.[21b]

CLINICAL AND LABORATORY FEATURES

The clinical manifestations of leptospirosis are protean. No constant feature characterizes any of the types in particular or the group in general. Thus, Weil's disease and canicola fever are indistinguishable clinically except in that the latter disease tends to be milder and much less fatal. Following an incubation period of one to two weeks, the onset of symptoms is commonly sudden but sometimes insidious. In other cases the disease may be almost asymptomatic.[24] When the onset is sudden, there may be a temperature elevation to 101 to 104 F., headache, vomiting, severe malaise, shaking chills, prostration, anorexia, severe myalgia, and arthralgia.[6d,g] Jaundice may be seen in only about 13% of cases,[25] and the severity of this sign is not believed to parallel the virulence of different strains of Lept. canicola.[20] Abdominal distress is observed more frequently in icteric patients. Conjunctival suffusion, iritis, and skin rashes are common, and hemorrhagic tendencies of variable degree are not infrequent. The most prevalent features in Minkenhof's series were acute onset, fever, shaking chills, vomiting, headache, dizziness, myalgia, disturbed sleep, and meningeal irritation.[7c] The chart of clinical features by Tievsky

20. Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: Canine Leptospirosis in United States, J. Am. Vet. M. A. **95**:710-729, 1939.

21. (*a*) Sacks, M. S.: The Problem of Leptospirosis, Editorial, Ann. Int. Med. **33**:481-486, 1950. (*b*) Alston, J. M.; Joshua, J. O.; Borg-Petersen, C.; Broom, J. C.; Stuart, R. D.; Field, H. I., and Edwards, J. T.: Discussion on Leptospirosis, Proc. Roy. Soc. Med. **42**:707-720, 1949.

22. Gochenour, W. S., Jr.; Yager, R. H., and Wetmore, P. W.: Antigenic Similarity of Bovine Strains of Leptospirae (United States) and Leptospira Pomona, Proc. Soc. Exper. Biol. & Med. **74**:199-202, 1950.

23. Weetch, R. S.; Colquhoun, J., and Broom, J. C.: Fatal Human Case of Canicola Fever, Lancet **1**:906-907, 1949.

24. Roos and others.[2] Meyer and others.[6b] Alston and others.[21b]

25. Rosenberg.[3] Alston and others.[21b]

and Schaefer [6e] is helpful, but Rosenberg's tabulation [3] appears most reliable, since it is based on analysis of 100 cases (Table 2). Cases with subacute or relapsing features may be confused with brucellosis, influenza, or tuberculosis.[26] The wide spectrum of symptoms may also simulate poliomyelitis, infectious mononucleosis, meningococcemia, influenza, typhoid, infectious hepatitis, and other diseases.

"Meningitic forms" of both canicola fever and Weil's disease have been described in which the dominant clinical features are those of meningeal irritation.[27] Several other reports stress the frequency with which meningeal irritation embraces the clinical picture in variable degrees, with abnormal spinal fluid findings.[28] The

TABLE 2.—*Frequency of Manifestations in Canicola Fever (Analysis of Approximately One Hundred Cases)**

Symptoms	Per Cent
Fever	100
Sudden onset	90
Prostration	87
Headache	80
Myalgia	70
Chills	52
Gastrointestinal symptoms	51
Mental symptoms	29
Signs	
Infected conjunctivae	48
Meningeal signs	48
Renal findings	39
Bradycardia	39
Hypotension	20
Bleeding tendency	20
Coated tongue	19
Respiratory findings	19
Sore throat	19
Rash	15
Icterus	13
Palpable liver	8
Lymphadenopathy	8
Herpes labialis	5
Palpable spleen	2.4
Laboratory Findings	
Rapid sedimentation rate	100
Albuminuria	75
Spinal fluid changes	42
Leucocytosis	41
Microscopic hematuria	36
Azotemia	32
Cylindruria	30

* From Rosenberg.[3]

26. Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: "Canicola Fever": A Professional Hazard, J. Am. Vet. M. A. **93**:332, 1938.

27. Buzzard and Wylie.[18a] Joe, A., and Sangster, G.: Canicola Fever: Report of 3 Cases of Meningitic Type in Human Subject, Edinburgh M. J. **58**:140-147, 1951.

28. (*a*) Cargill, W. H., Jr., and Beeson, P. B.: The Value of Spinal Fluid Examination as a Diagnostic Procedure in Weil's Disease, Ann. Int. Med. **27**:396-400, 1947. (*b*) Snapper, I.; Chung, H. L.; Chu, I., and Chen, K. C.: Preliminary Observations on Human, Canine and Murine Leptospirosis in North China, Chinese M. J. **58**:408-426, 1940. (*c*) Beleke, H., and Bandau, R.: Zwei Fälle von Canicolafieber mit rezidivierender Pleocytose und seltener Augenkomplikation, Nervenarzt **21**:446-447, 1950. (*d*) Laurent, L. J. M.; Norris, T. St. M.; Starks, J. M.; Broom, J. C., and Alston, J. M.: Four Cases of Leptospira Canicola Infection in England, Lancet **2**:48-51, 1948.

importance of this phenomenon is emphasized by the statement that "mild meningitis is the most prominent feature in two-thirds of the cases found." [21b] Ocular manifestations, such as iritis, iridocyclitis, conjunctivitis, and photophobia, concomitant with neurological features, are relatively common, and this curious combination is of diagnostic value.

Hepatomegaly, when observed, is said to occur only in the deeply jaundiced patients. Splenomegaly is relatively rare.

Of interest is the fact that no case of chronic nephritis due to Lept. canicola is on record, despite the frequency of acute nephritis. Acute hemorrhagic nephritis may occur.[29] Varying degrees of azotemia, oliguria, and anuria are described in cases with renal involvement. Epistaxis is fairly common and is usually a manifestation of hemorrhagic diathesis. Bradycardia, particularly in jaundiced patients, has been frequently described but usually in a relative sense, i. e., a pulse rate in disproportion to the degree of fever.

In the clinical laboratory studies the most important procedures include the hemogram, determination of the sedimentation rate and icterus index, liver-function tests, urinalysis, spinal fluid examination (in presence of meningitic features), dark-field examination of blood and urine for leptospirae, blood and urine cultures, agglutination-lysis tests, and injections of blood or urine of the patient into guinea pigs and hamsters. Obviously, strategic timing in obtaining specimens is of the essence in yielding diagnostic results.

The hemogram commonly exhibits leucocytosis, with a shift to the left, but not infrequently these features are absent. The sedimentation rate is invariably elevated and usually very high. Since, as previously stated, jaundice is described in only 13% of cases, the icterus index may often be normal. In such cases serum bilirubin values may be helpful. Impaired liver function, as measured by cephalin-flocculation and thymol-turbidity tests, is not uncommonly demonstrated, even in the absence of clinical or subclinical icterus.

Albuminuria is said to occur in 75% of cases,[3] while microhematuria and urinary casts are seen in approximately one-third, usually with some degree of azotemia.

In nearly all patients with meningitic symptoms, spinal fluid examination discloses variable pleocytosis. Initially polymorphonuclear cells predominate, but later lymphocytes may be in the majority.[6g] A slight increase in protein is the rule.

It has been repeatedly stated that dark-field examination of the blood for Lept. canicola is generally unsatisfactory, since the yield is not only poor but fraught with the danger of false interpretation due to so-called pseudospirochetes.[30] The commonly used procedure is dark-field examination of a neutral, centrifuged fresh urine specimen obtained between the 10th and the 13th day of the disease. It is said that the organism can frequently be demonstrated in this fashion. However, surprisingly few case reports in the literature are confirmed by actual demonstration of the leptospirae. For example, Borg-Petersen [21b] stated that leptospirae could be demonstrated in only 81 of a series of 808 patients with leptospirosis (10%).

Blood or urine cultures are of confirmatory value only, since five to six weeks may be required for growth of the organism.[6g] For best results, Schüffner's modi-

29. Bruno and others.[6d] Dhont and others.[9c] Meyer and others.[26]

30. Schultz, E. W.: Pseudospirochetes Derived from Red Blood Cells, J. Lab. & Clin. Med. **8**:375-381, 1923. Gowen, G. H.: Pseudospirochaetes in Blood, Illinois M. J. **89**:294-296, 1946.

fication of Verwoort's medium, a highly buffered peptone-serum preparation, is recommended.

The agglutination-lysis test of Schüffner and Mochtar,[5a] or one of its modifications, is the most reliable and conclusive of all laboratory procedures in the diagnosis of canicola fever. While the test is possessed of a high degree of diagnostic accuracy for leptospiral infections in general, there is frequently cross agglutination between Lept. canicola and Lept. icterohemorrhagiae or Leptospira hebdomadis [28b] in the first few weeks of the disease.[21b] In fact, heterologous reactions may exceed homologous reactions, so that it may be impossible to accurately distinguish Weil's disease from canicola fever at this stage. On repeated testing, the homologous reactions invariably dominate sooner or later, however. For early identification of the true serologic type, the absorption test of Ruys and Schüffner [31] is sometimes used.

There is no one titer which is diagnostic of present infection. Therefore, it is most essential to obtain sera at regular intervals throughout the disease in an effort to demonstrate a rising titer, which is the most reliable phenomenon indicating the presence of active infection.[32] A maximum titer may occur any time between two and eight weeks. In two or three years the titer may fall to 1:300 and persist for many years.[6g] In other instances detectable antibodies may disappear in one month after the maximum titer is reached. False-positive and anamnestic reactions are rare.

The ideal subject for animal inoculation is said to be the young hamster (3 to 4 weeks old),[33] especially the golden hamster,[34] since guinea pigs and mice are quite resistant to Lept. canicola infection. Injection of the patient's urine before the fourth week (or blood during the first week) is regularly followed by the animal's death in 2 to 12 days from the disease. At autopsy hemorrhagic lesions may be found in the lungs.

DIAGNOSIS

It is virtually impossible to make a clinical diagnosis of canicola fever, since the clinical features are more or less identical with those of Weil's disease. Diagnosis, therefore, rests primarily on suspicion of the disease, followed by the agglutination tests, cultural methods, or both, as previously described. Suspicion of the disease should be aroused in the presence of fever with shaking chills, albuminuria, meningeal signs or symptoms, conjunctival suffusion, history of direct or indirect contact with dogs, headache, myalgia, gastrointestinal upsets, unexplained bleeding, skin rash, or jaundice. Any combination of these findings, in the absence of an obvious diagnosis, justifies use of an agglutination-lysis test for leptospirosis as a minimum laboratory procedure. However, the aforementioned clinical features are of distinct value collectively to enhance the clinician's index of suspicion.

31. Ruys, A. C., and Schüffner, W. A. P.: De waarde van absorptieproeven voor de serologische diagnose van verschillende Leptospira-infecties, Nederl. tijdschr. geneesk. **78**:3110-3114, 1934.

32. Tiffany, E. J., and Martorana, N. F.: Leptospirosis in New York City: A Serological Survey, Am. J. Hyg. **36**:195-204, 1942.

33. (*a*) Tiffany and Martorana.[32] (*b*) Larson, C. L.: Experimental Leptospirosis in Hamsters (Cricetus Auratus), Pub. Health Rep. **59**:522-527, 1944.

34. Randall, R., and Cooper, H. K.: The Golden Hamster (Cricetus Auratus) as a Test Animal for the Diagnosis of Leptospirosis, Science **100**:133-134, 1944.

Lengthy discussions on differential diagnosis are obviously nebulous, since "the diagnosis of canicola fever certainly cannot be established, owing to lack of a constant well-defined clinical syndrome, until laboratory evidence is obtained." [6g]

COMPLICATIONS

Unlike Weil's disease, complications in canicola fever are infrequent and relatively mild. They include myocarditis, psychosis, iritis, iridocyclitis, vitreous opacity, and muscular paralysis. In the two fatal cases for which pathologic reports were available, death was due to terminal uremia from acute nephritis superimposed on preexisting renal disease (polycystic kidneys [21b] in one instance, and chronic nephritis [23] in the other).

In the case report of Turrell and Hamburger,[6k] focal skeletal muscle degeneration was demonstrated for the first time in canicola fever, a change which appears to be identical with lesions described in Weil's disease.[35] Whether this represents a complication or a pathologic feature of the disease depends upon future case reports, but in favor of the latter is the description of this lesion in dogs.[36]

TREATMENT

At present penicillin is the drug of choice in treatment of canicola fever, although results are variable. Patients receiving penicillin early in the disease generally respond very favorably, and in at least one case treatment with the drug was considered lifesaving,[6k] the dose being 100,000 units every three hours. The action of penicillin is probably leptospirostatic.[37] Alston and Broom [37c] recorded the important observation that penicillin does not impair antibody formation. The value of other antibiotics in this disease is not as yet properly assessed, but more recent reports suggest that both aureomycin and terramycin are effective, especially in Weil's disease.[38] Use of antiserum is probably unnecessary. The field of prophylactic vaccines has not been explored, although it should be in view of the success

35. Sheldon, W. H.: Lesions of Muscle in Spirochetal Jaundice (Weil's Disease; Spirochetosis Icterohemorrhagica), Arch. Int. Med. **75**:119-124 (Feb.) 1945. Jeghers, H. J.; Houghton, J. D., and Foley, J. A.: Weil's Disease: Report of a Case with Postmortem Observations and Review of Recent Literature, Arch. Path. **20**:447-476 (Sept.) 1935.

36. Dacorso Filho, P.: Contribucão à anatomia patológica da Leptospirose icterhemorrágica no cão, Bol. Soc. brasil med. vet. **14**:7, 1945.

37. (*a*) Chang, S. L.: Studies on Leptospira Icterohemorrhagiae: A Critical Study of the Effect of Penicillin on Leptospira Icterohemorrhagicae in Vitro and on Leptospirosis in Guinea-Pigs, J. Clin. Invest. **25**:752-760, 1946. (*b*) Wylie, J. A. H., and Vincent, E.: The Sensitivity of Organisms of the Genus Leptospira to Penicillin and Streptomycin, J. Path. & Bact. **59**:247-254, 1947. (*c*) Alston, J. M., and Broom, J. C.: The Action of Penicillin on Leptospira and on Leptospiral Infections in Guinea-Pigs, Brit. M. J. **2**:718-719, 1944.

38. Heilman, F. R.: Aureomycin in the Treatment of Experimental Relapsing Fever and Leptospirosis Icterohaemorrhagica (Weil's Disease), Proc. Staff Meet., Mayo Clin. **23**:569-573, 1948. Lurie, I.: Leptospirosis Ictero-Hemorrhagica (Weil's Disease) Treated with Aureomycin: Report of a Case, Acta med. orient. **8**:188-189, 1949. Brainerd, H.; Lennette, E. H.; Meiklejohn, G.; Bruyn, H. B., Jr., and Clark, W. H.: The Clinical Evaluation of Aureomycin, J. Clin. Invest. **28**:992-1005, 1949. Liebowitz, D., and Schwartz, H.: Leptospiral Infection in Man Treated with Terramycin: Report of a Case, J. A. M. A. **147**:122-123 (Sept. 8) 1951.

of vaccines in Weil's disease.[39] It may be that protection against canicola fever is achieved by vaccination against Weil's disease.[40]

The remaining therapy of canicola fever is symptomatic and supportive. Isolation is justifiable until man-to-man transmission is conclusively disproved.

REPORT OF CASES

CASE 1.—The patient, a man aged 43, was first seen Feb. 10, 1950, giving a history of insidious jaundice developing during the previous two weeks, accompanied with fever, shaking chills, amber-colored urine, vague soreness in the epigastrium, severe headache, anorexia, "red eyes," severe aches in muscles, and a weight loss of about 15 lb. (6.8 kg.) during this period.

The previous history revealed no serious illnesses or surgical procedures. His occupation was boiler fireman.

The family history disclosed that two children (Cases 3 and 4) had been jaundiced with similar but less severe symptoms about one month prior to onset of the patient's complaints.

Complete physical examination revealed a seriously ill man, obviously underweight and deeply jaundiced. There was moderate conjunctival suffusion. However, temperature, pulse rate, blood pressure, and respirations were normal. Moderate nuchal rigidity was in evidence. Definite epigastric tenderness was noted, and the liver edge descended 6 cm. below the right costal margin. The calf muscles were extremely tender to pressure. The remaining physical findings were normal.

Roentgen examination of the chest, esophagus, stomach, and duodenum showed an essentially normal condition. The hemoglobin concentration was 14.4 gm. per 100 cc.; erythrocytes numbered 4,720,000, and leucocytes, 5,400, with a normal differential count. The sedimentation rate was 61 mm. in one hour (Westergren method). The icterus index was 134 units. A cephalin-flocculation liver-function test gave a 4+ reaction. The prothrombin time was normal. Alkaline phosphatase was 2.7 Bodansky units, and a serologic test for syphilis gave a negative reaction. Urinalysis showed albumin (2+), but results were otherwise entirely normal.

The patient was hospitalized from Feb. 15 to March 15, 1950, and was treated for infectious hepatitis, without administration of antibiotics or sulfonamides. His condition gradually improved to the extent that the icterus index fell to 60 units and the reaction to the cephalin-flocculation liver-function test decreased to 3+. The liver edge receded 3 cm., and the patient gained 4 lb. (1.8 kg.).

At the end of this patient's hospital stay, it was discovered that he had been living in conditions of squalor, that rats infested his home, and that the family dog had previously been sick. Therefore, agglutination tests for leptospirosis were carried out on six other members of the family who were currently ill. (The specimens were taken March 15, but results were not reported until April 5, 1950.) This patient's serum was found to agglutinate Lept. icterohemorrhagiae in a titer of 1:128 and Lept. canicola in a titer of 1:512. In the absence of any signs of active infection and in view of his obvious clinical improvement, antibiotic therapy at this stage was considered useless. Agglutination tests were repeated on June 6, 1950. The titer for Lept. canicola had fallen to 1:32, and the titer for Lept. icterohemorrhagiae was now "doubtful."

CASE 2.—This patient, the 34-year-old wife of the first patient (Case 1), was first seen Feb. 20, 1950, giving a history of rapidly developing jaundice during the previous four days, accompanied with severe headache, spiking fever with shaking chills, prostration, severe myalgia (chiefly in the lower back and calf muscles), vomiting, severe epigastric pain, amber-colored urine, and burning sensation in the eyes with photophobia.

Except for her having had seven children (all normal deliveries), the patient's previous history was noncontributory.

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39. Das Gupta, B. M.: Observations on Some Immunological Aspects of Leptospira Icterohemorrhagiae: Development of Active Immunity in Many Following Injection of Leptospira Vaccine, Indian M. Gaz. **77**:28, 1942.

40. Smith, J.: Vaccination of Guinea-Pigs and Human Beings Against Leptospiral Infections, J. Hyg. **37**:261-270, 1937.

Physical examination revealed a moderately obese patient, acutely ill, with temperature of 100.4 F., pulse rate of 80, and normal respirations. The blood pressure was normal. The skin and scleras were jaundiced, Grade II (grading on the basis of I to IV). There was mild injection of the conjunctivae. The mouth was edentulous. The abdomen was exquisitely tender, especially in the upper right quadrant, where the liver edge descended 5 cm. below the right costal margin. The spleen was not palpable. Results of a complete physical examination were otherwise normal.

A roentgenogram of the chest was normal. The hemoglobin concentration was 13.3 gm. per 100 cc.; erythrocytes and leucocytes numbered 4,170,000 and 5,600 per cubic millimeter, respectively. The differential count was normal. The sedimentation rate was 50 mm. in one hour (Westergren method). The icterus index was 62 units. A cephalin-flocculation liver-function test showed a 4+ reaction, but the prothrombin time was within normal limits. Results of urinalysis were normal except for a 2+ reaction for albumin. A serologic test for syphilis gave a negative reaction.

The patient was hospitalized from Feb. 21 to May 6, 1950, during which time her illness pursued a stormy course. During the first two weeks of hospitalization, the fever had largely subsided, yet the patient's symptoms were very severe. She complained of excruciating frontooccipital headache, and there was definite nuchal rigidity, but no other neurological signs appeared. The patient refused diagnostic spinal tap. The headache did not respond to administration of the usual analgesics. During the second to fifth hospital weeks lumbar backache and muscle pains were very severe. The myalgia was severest in the calves. In view of backache, severe dyspepsia, and epigastric distress, roentgenograms of the dorsal spine and cholecystograms were made on March 28. The findings were normal. Catheterized urine showed 1+ and 2+ reactions for albumin during the second and third weeks of hospitalization, but the sediment was normal. The blood urea was only 21.6 mg. per 100 cc. during the acute stage of the disease.

On April 5, results of agglutination tests for Lept. canicola and Lept. icterohemorrhagiae were reported positive in dilutions of 1:256 and 1:32, respectively. Thereafter, the patient was treated with aqueous procaine penicillin, 500,000 units every 12 hours intramuscularly, until her dismissal from the hospital on May 6. Administration of aureomycin in 500-mg. doses every six hours was started with the penicillin therapy but had to be discontinued because the drug induced vomiting. Jaundice had subsided after the first three weeks of hospitalization. The result of the cephalin-flocculation liver-function test was reported as 3+ on April 5.

After this patient's dismissal from the hospital, results of repeat agglutination tests were reported as follows: Lept. canicola, 1:4,000; Lept. icterohemorrhagiae, 1:32. The patient had a prolonged, difficult convalescence. She constantly complained of weakness, easy fatigue, and epigastric pain and tenderness. Cephalin-flocculation liver-function tests were repeated in May and June, 1950, and again in February, 1951. On all three occasions the reaction was reported as 3+. On the last occasion the patient complained that her epigastric pain was unusually severe, and the liver edge could be palpated 4 cm. below the right costal margin with exquisite tenderness. Her temperature was 99.6 F. The icterus index was 9.5 units. Results of urinalysis were normal. The patient later proved to be four weeks pregnant. At the time of this report (Aug. 20, 1951), she had generally improved, and pregnancy was progressing without incident, although her hepatomegaly persisted.

CASE 3.—The patient, a 5-year-old son of the above two patients (Cases 1 and 2), entered the hospital on Feb. 21, 1950, with a history of nausea, vomiting, frontal headache, epigastric distress, amber-colored urine, myalgia, and intermittent fever during the preceding two weeks. The child's parents described this as a recurrence of a similar attack early in the preceding month, during which the symptoms were severer and accompanied with "yellow jaundice." A physician had not been consulted at that time. On entering the hospital, the patient was symptom free, having been admitted for isolation purposes.

The pulse rate, temperature, and respirations were normal, and a complete physical examination disclosed no abnormalities except a palpable liver edge descending 3 cm. below the right costal margin with only slight tenderness.

A cephalin-flocculation liver-function test gave a 3+ reaction, and the icterus index was 30.2 units. Results of urinalysis were normal. The urine was tested for bile daily for 10 days, and the reactions proved consistently negative. Results of agglutination tests were reported on

April 26 as "doubtful" for Lept. canicola and negative for Lept. icterohemorrhagiae, but the serum specimen was turbid and considered unsatisfactory for testing.

This patient was discharged from the hospital March 13, at which time the liver was no longer palpable.

CASE 4.—The patient, a 7-year-old daughter of the first two patients (Cases 1 and 2), was hospitalized on Feb. 21, 1950, despite lack of complaints, for isolation purposes. However, during early January, 1950, she had had an illness of two weeks' duration characterized by definite jaundice, fever, shaking chills, myalgia, anorexia, and "inflamed eyes," as described by her parents.

The temperature, pulse rate, and respirations were normal, and a complete general physical examination revealed no abnormalities. Results of urinalysis were normal, and a daily test showed no bile in the urine for 12 days. A cephalin-flocculation liver-function test was reported as showing a 2+ reaction. Results of agglutination tests were reported as "doubtful" for Lept. canicola and negative for Lept. icterohemorrhagiae on April 26, but this serum specimen was also turbid and considered unsatisfactory for testing.

The patient was discharged from the hospital on March 13.

CASE 5.—The patient, a 9-year-old daughter of the first two patients (Cases 1 and 2), was admitted to the hospital Feb. 21, 1950, with complaints of fever, shaking chills, vomiting, epigastric pain, anorexia, severe occipital headache with stiffness of the neck, moderate jaundice, myalgia, and amber-colored urine. These symptoms were sudden in onset seven days prior to admission and were still severe.

Physical examination revealed an acutely ill patient whose temperature was 103.4 F. The pulse rate was 120 and the respiration rate 22 per minute. The blood pressure was normal. Moderate conjunctival suffusion and definite nuchal rigidity were noted. A complete physical examination otherwise revealed normal findings. The liver edge was not palpable.

Urinalysis, including several daily tests for bile, gave negative results. However, the icterus index was 13.7 units (acetone method), and the reaction to the cephalin-flocculation liver-function test was 3+.

Because of spiking fever, this patient received a long-acting penicillin preparation, 400,000 units intramuscularly every 24 hours for three days, after which she remained afebrile and improved rapidly.

The patient recovered and was dismissed from the hospital on March 15, at which time serum was sent for agglutination tests. On April 5, 1950, results of agglutination tests were reported as positive for Lept. canicola and Lept. icterohemorrhagiae in dilutions of 1:256 and 1:8, respectively.

CASE 6.—The patient, an 11-year-old son of the first two patients (Cases 1 and 2), entered the hospital Feb. 21, 1950, with a history of fever, shaking chills, vomiting, anorexia, severe myalgia, frontal headache, weakness, epigastric pain, mild icterus, and amber-colored urine of seven days' duration. The onset had been sudden.

On physical examination the temperature was 100 F. The pulse rate was 90 per minute, and respirations were normal. The patient appeared acutely ill. The liver edge descended 1 cm. below the right costal margin and was moderately tender. Physical findings were otherwise normal.

A cephalin-flocculation liver-function test gave a 4+ reaction, and the icterus index was 14.6 units. Urinalysis showed albumin (2+), but results were otherwise normal, including those on tests for bile daily for several days. The sedimentation rate was 60 mm. in one hour (Westergren method).

The patient improved rapidly after hospitalization, without penicillin therapy. He was dismissed March 9. On April 5, 1950, agglutination tests (on serum taken March 15) were reported as showing positive reactions for Lept. canicola in a dilution of 1:32 and negative reactions for Lept. icterohemorrhagiae.

CASE 7.—The patient, a 13-year-old son of the first two patients (Cases 1 and 2), was hospitalized for isolation purposes on Feb. 21, 1950. He was symptom free.

On physical examination the temperature was 101 F., but the pulse rate and respirations were normal. The liver edge was palpable 2 cm. below the right costal margin without tenderness. Physical findings were otherwise normal.

Urinalysis gave normal results except for a trace of albumin. The reaction to a cephalin-flocculation liver-function test was only 2+. The icterus index was 3 units.

On the third hospital day, albuminuria (1+) was noted and bile appeared in the urine. Low-grade fever continued until the ninth hospital day, after which the patient remained afebrile. There were no symptoms at any time. On April 5, 1950, reactions to agglutination tests (on serum taken March 15) were reported as positive for Lept. icterohemorrhagiae and Lept. canicola in dilutions of 1:32 and 1:128, respectively. The patient had been discharged on March 9 and was considered recovered.

CASE 8.—The patient, a 14-year-old son of the first two patients (Cases 1 and 2), was admitted to the hospital for isolation purposes on Feb. 21, 1950, with no complaints.

A thorough physical examination, including determination of the pulse rate, temperature, and respiration rate, gave entirely negative or normal results.

Results of urinalysis were normal except for a trace of albumin. Daily urine tests for bile gave negative reactions on 12 occasions.

On Feb. 26, a cephalin-flocculation liver-function test showed a 4+ reaction and the icterus index was 21 units. These tests were performed because the liver edge had become palpable 3 cm. below the right costal margin with definite tenderness and the patient had displayed nausea, anorexia, and epigastric discomfort. He remained afebrile.

On April 5, 1950, results of agglutination tests (on serum taken March 15) for Lept. icterohemorrhagiae and Lept. canicola were positive in dilutions of 1:16 and 1:512, respectively. The patient had been discharged as "recovered" on March 15.

CASE 9.—The patient, a 16-year-old son of the first two patients (Cases 1 and 2) was hospitalized Feb. 21, 1950, with a history of nausea, epigastric pain, severe myalgia, amber-colored urine, fever, shaking chills, severe headache, and "stiff neck" of four days' duration.

On physical examination the patient appeared acutely ill, with a temperature of 101.6 F., a pulse rate of 100 per minute, and a respiration rate of 22 per minute. The scleras were definitely icteric and injected. Definite nuchal rigidity was in evidence, but no other signs of meningeal irritation could be elicited. The liver edge descended 3 cm. below the right costal margin and was quite tender.

Urinalysis performed on his admission to the hospital gave normal results. The icterus index was 51 units, and the reaction to a cephalin-flocculation liver-function test was 4+.

The patient was given aureomycin, 250 mg. three times a day, after the third hospital day because symptoms were becoming progressively worse with spiking fever (temperature elevation to 102 F.). On the ninth hospital day bile appeared in the urine. The patient gradually improved, was dismissed from the hospital on March 10, and was considered recovered.

On April 5, 1950, agglutination tests (on serum taken March 15) for this patient were reported as showing a positive reaction for Lept. icterohemorrhagiae and Lept. canicola in dilutions of 1:8 and 1:1,024, respectively.

EPIDEMIOLOGIC INVESTIGATION

Obviously, the clinical features of jaundice, hepatomegaly, impaired liver function, epigastric pain, nausea, vomiting, fever, and epidemicity portended a diagnosis of viral hepatitis. Unfortunately, the disease in all the patients was so diagnosed and treated until more thorough investigation of the living conditions of this family disclosed the presence of rats and a recently sick dog, thus arousing the suspicion of leptospirosis. The dog had been allowed to forage and delighted in catching and chewing up rats. Further, it was the practice of the entire family, whose crowded living quarters consisted of an old converted boxcar, to drink water from a pail with a communal dipper. Water was obtained from a nearby hydrant. Occasionally the pail was left on the floor. The male bulldog was an intimate pet of the entire family and was caught drinking from the family water pail on occasion. The male dog's common practice of licking his genitalia readily explains one of many ways in which food and water may have thereby been contaminated with leptospirae. The dog

appeared healthy when the living quarters were inspected by public health officials. A serum specimen was obtained, after which the animal was killed. A complete autopsy revealed typical lesions of interstitial nephritis, and leptospirae were demonstrated histologically with Levaditi's stain. The dog's serum was shown to agglutinate Lept. canicola in a dilution of 1:128, but agglutination for Lept. icterohemorrhagiae was reported as "doubtful." (The presence of agglutinins, no matter how low the titer, is indication that the dog had at some time in life come into contact with the organism.[21a]) The diagnosis of Lept. canicola infection in the dog was, therefore, considered unequivocal.

Of some interest was the fact that toilet facilities for this family consisted of an outdoor latrine in which excreta were pyramided above the level of the toilet seat. The door was ajar, deeply embedded in ice. What role this situation played in the epidemic is only speculative.

While the public health barriers to spread of viral hepatitis were meager in this poverty-stricken area, investigation of the neighborhood revealed no other cases of jaundice or acute infectious disease. This further enhanced suspicion of the presence of canicola fever in the family.

COMMENT

The diagnosis of canicola fever could have been established in these cases with much greater ease if (1) the disease in the dog had been discovered earlier, (2) several serum specimens had not been contaminated when taken or broken on arrival at the special bacteriology laboratories of the United States Public Health Service at Chamblee, Ga.,[41] (3) attempts at isolation of the organisms from the urine could have been made earlier in the disease, (4) rising titers for Lept. canicola could have been demonstrated in every case, and (5) antibodies against Lept. canicola could have been demonstrated in every case. On the other hand, the diagnosis is believed proved beyond all reasonable doubt on the basis of the following facts:

1. Canine leptospirosis was proved in the family pet.

2. The typical combination of conjunctival suffusion, meningeal irritation, muscle pain and tenderness, and positive reactions to agglutination tests were present in five patients (Cases 1, 2, 5, 7, and 9).

3. A rising titer in one patient (Case 2), indicating active canicola fever, and a falling titer in another patient (Case 1), indicating subsiding infection or convalescence, were demonstrated.

4. Viral hepatitis is excluded by the above data and by the following laboratory determinations made during the icteric phase of the disease:

   (*a*) Decided elevation of the erythrocyte sedimentation rate (determined in Cases 1, 2, and 6)

   (*b*) Normal blood alkaline phosphatase (determined in Case 1)

   (*c*) Normal prothrombin levels (determined in Cases 1 and 2)

   (*d*) The occurrence of shaking chills in six patients (Cases 1, 2, 4, 5, 6, and 9), said to be a rare symptom in viral hepatitis[42]

41. For the benefit of those who may be equally unaware of the practical difficulties in collection and shipping of specimens the following suggestions are made: *A*, take one specimen as early in the disease as possible and a second specimen about two weeks later, etc. *B*, serum must be sterile, free from turbidity and hemolysis. Minimum quantity is 2 cc of serum. *C*, tubes must be tightly sealed and wrapped in double containers.

42. Harrison, T. R.: Principles of Internal Medicine, Philadelphia, The Blakiston Company, 1950, p. 1083.

Since hamsters were not available, guinea pigs were inoculated with urine specimens from three patients (Cases 1, 2, and 9). These animals survived without symptoms. Had hamsters been used, they may well have acquired the disease and led to isolation of Lept. canicola.

In view of the foregoing clinical, laboratory, and epidemiologic evidence, there appears to be no necessity for considering a detailed differential diagnosis in this group of cases. While significant titers could not be demonstrated in Cases 3, 4, and 5, presumptive evidence of past or present infection is apparent in the anamnesis and clinical and laboratory findings. While in Cases 3 and 4 the serum specimens were unsatisfactory for testing, the low titer for Lept. canicola in Case 5 may be explained on the basis of timing. The latter point is dramatically illustrated by the patient of Tievsky and associates,[6e] in whom the titer fell from 1 : 10,000 to 1 : 1,000 in only five days. Titers may be extremely variable, ranging from very low dilutions to 1 : 1,000,000 or higher. The high degree of serologic specificity minimizes the importance of high titers, although changing titers are important indices of past or present infection. Moreover, the time of disappearance of detectable antibodies is entirely unpredictable, varying from four weeks to many years. The use of formalinized antigen in performing agglutination tests in the present series results in lower titers, but results are considered even more specific than those which obtain from living cultures, in the opinion of some workers. That the use of formalinized antigen may yield very low or even negative titers is suggested by a recent case report in which agglutinations with the use of dead organisms were reported as negative, while the use of living organisms as the antigen yielded positive titers in dilutions of 1 : 16,000 for Lept. icterohemorrhagiae and 1 : 2,048 for Lept. canicola in the same patient's serum. Specimens were drawn only three days apart.

This epidemic is unique in four respects:

1. It is the largest epidemic reported in one family.
2. Some evidence of either jaundice or liver involvement was present in all cases.
3. It is the largest group of cases thus far reported in the American literature.
4. The occurrence of this disease in six children under 15 years of age is considered relatively rare. The relatively mild to minimal symptoms in these instances suggest that children may be more resistant than adults to the infection.

The prolonged convalescence in Cases 1 and 2 is not unusual since "in some 45 per cent of cases convalescence was not completed until after two, three or even four months."[3] The icterus index in Case 1 is the highest recorded in the literature to date.

SUMMARY AND CONCLUSIONS

Canicola fever is a much commoner disease than was previously realized. A review of the world literature discloses a disproportionately low incidence of this disease in the United States, when compared with that in other countries. Including the first two case reports in 1939,[6d] a total of only 16 cases is described in the American literature. The present report of 9 cases occurring in one family brings this total to 25 cases. Because precise diagnosis is impossible without specific agglutination tests, there is great need for increased laboratory facilities throughout the nation for performance of these tests.

The diagnosis of canicola fever in the present series of nine cases is believed established beyond all reasonable doubt by virtue of positive results on agglutination

tests and/or clinical and laboratory determinations and by studies on the family dog, which was proved to have canine leptospirosis serologically and by demonstration of Lept. canicola in the kidneys at necropsy.

Agglutination tests for leptospirosis should be included in the general group of agglutination tests performed in all cases of unexplained fever, jaundice, and myalgia, especially when accompanied with signs of meningeal irritation, conjunctivitis, or albuminuria.

It is hoped that the present study will stimulate increased awareness of this disease entity among clinicians because specific therapy is available.

The following persons assisted in this study: Melvin E. Koons, M.S., M.P.H., Associate Professor of Public Health and Preventive Medicine, and Robert G. Fischer, Ph.D., Associate Professor of Bacteriology; Assistant Director, Medical Technology Training Program, University of North Dakota School of Medicine; Martin Frobischer Jr., Sc.D., Bacteriologist-in-Charge, Communicable Disease Center, Special Bacteriology Laboratories, and Martha K. Ward, Sc.D., Bacteriologist-in-Charge, Special Bacteriology Laboratories, Communicable Disease Center, United States Public Health Service, Chamblee, Ga.

News and Comment

GENERAL NEWS

Radioactive Cortisone.—Radioactive cortisone for use in medical research will be manufactured with the aid of funds from the National Institute of Arthritis and Metabolic Diseases, Dr. Russell M. Wilder, Director of the Institute, announced. The Institute is under the supervision of the Public Health Service of the Federal Security Agency. The radioactive cortisone has not been produced hitherto in sufficient quantity for research studies. It will contain radioactive carbon. This will "tag" the cortisone so that it can be traced through the bodies of experimental animals to learn how it produces its effects in health and disease.

MEETINGS

Mississippi Valley Medical Society.—The 17th annual meeting of the Mississippi Valley Medical Society will be held Oct. 1, 2, and 3, 1952, at the Jefferson Hotel, St. Louis. The ninth annual meeting of the American Medical Writers' Association will be held Oct. 1 at the same place.

Books

Surgical Care: A Practical Physiologic Guide. By Robert Elman, M.D. Price, $8. Pp. 586, with 18 illustrations. Appleton-Century-Crofts Company, Inc., 35 W. 32d St., New York 1, 1951.

The author includes in the term "surgical care" not only preoperative diagnosis and preparation and postoperative care but also complete rehabilitation of the patient. He deals with the factors of basic science, knowledge of bedside medicine, physiologic mechanisms, and psychologic insight involved in achieving the goal of full recovery of the patient.

The material presented, as indicated by the subtitle, is intended to be practical. Physiologic principles are constantly emphasized in contrast to the surgical care directed by clinical impressions. A positive program based on sound physiologic and biochemical knowledge is outlined. The material covered includes not only what one would expect pertaining to basic preoperative and postoperative care but also excellent chapters on psychogenic factors in surgery, anesthesia, nutrition in surgery, and chemotherapy in surgery, shock, and burns.

The book reads easily. Pertinent and very excellent summaries of known physiologic and biochemical facts are carried to their practical conclusion in the treatment of the patient. All physicians who in any way deal with the surgical patient should find this book very useful. House officers especially (who play such an important part in the care of the surgical patient) should find here much of value in grounding themselves in scientifically sound and practical management of the surgical patient.

Visceral Innervation and Its Relation to Personality. By Albert Kuntz, Ph.D., M.D. Price, $4.50. Pp. 160, with 31 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1951.

No one is better fitted to write about the autonomic nervous system than Dr. Kuntz. In this little book he not only reviews in modern terms the anatomical arrangements but correlates them with physiological effects. Thus, a tie-up is effected between anatomy and chemical mediation of nerve impulse, endocrine influences in visceral function, temperature regulation, water metabolism, etc. The book seems valuable from the physician's standpoint in bridging the gap between basic science and clinical physiology. The paper and print are of fine quality, and there are an index and a bibliography.

Your Diabetes: A Complete Manual for Patients. Second edition revised. By Herbert Pollack, M.D., and Mary V. Krause, M.S. Price, $3. Pp. 212. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York 16, 1951.

Books on diabetes for patients began to appear at least as long ago as 1918, when Joslin's "A Diabetic Manual" was first printed. Ever since, a variety of books of this general character have appeared, carefully prepared by experts in different parts of the country and all designed to give practical information to diabetic patients and their families.

"Your Diabetes" is one of the latest in the series. It tells its story simply, clearly, and in a thoroughly understandable way. It promises to be successful, for, after an initial edition, a second and completely revised edition was necessary a few months later. It is worth reading.

A Classified Bibliography of Gerontology and Geriatrics. By Nathan W. Shock. Price, $15. Pp. 599. Stanford University Press, Stanford University, Calif., 1951.

As the title indicates, this book is a source of classified bibliographic data. Those interested in sources of information concerning various phases of gerontology and geriatrics will find this classified bibliography useful.

Clinical Practice in Infectious Diseases: For Students, Practitioners, and Medical Officers. Fourth edition. Edited by E. H. R. Harries, M.D. (Lond.), F.R.C.P., and M. Mitman, M.D. (Lond.), F.R.C.P., with collaboration of Ian Taylor, M.D. (Lond.), M.R.C.P. Price, $6.50. Pp. 728, with 68 illustrations, 20 colored. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

Simply and clearly written and stripped of superfluous verbiage, this is an admirable short treatise on infectious disease. The first hundred-odd pages deal well with general matters, such as infection and resistance, allergy, serum reactions, transmission, general principles of diagnosis, and epidemiology. These sections should be particularly useful. The descriptions of individual diseases are vivid and adequate, and the excellent color photographs of eruptions, bacterial cultures, etc., add greatly to the value of the text. As is usual with the British, a note of conservatism is sounded here and there; in therapy stress is placed on that which has been thoroughly tried and found useful.

A Course in Practical Therapeutics. Second edition. By Martin Emil Rehfuss, M.D., and Alison Howe Price, M.D. Price, $15. Pp. 938, with illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

The title of this book might well be "Practical Diagnosis and Therapeutics," as it includes the chief facts pertaining to causes, symptoms, differential diagnosis, and laboratory diagnosis of the principal diseases, as well as their treatment. The volume is divided into four sections dealing with general therapeutic principles, symptomatic therapy, treatment of specific disorders, and special treatment. The data on a single disease are often presented by visual means on a single page. The collaboration of 17 authors adds authority and strength to certain specialized fields. The book is well planned; the material is authoritative and up to date and represents a complete coverage of the subject, including even atomic warfare. It will appeal chiefly to the general practitioner, who can scarcely fail to appreciate the readable and easily assimilated presentations designed for reference with the minimum expenditure of time.

Medical Milestones. By Henry J. L. Marriott, M.D. Price, $3.50. Pp. 293. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1952.

Dr. Marriott has undertaken a rather formidable task, that of encompassing in a single volume the high points of medical progress in the past decade and setting them down in simple enough form to be understood by the lay public. On the whole, he has done a very creditable job, although it is hardly likely that all the material will be easily digested by those without medical training. His subject matter includes the whole range of antibiotics now in common use, cardiac surgery, antithyroid drugs, the Rh factor, BAL (dimercaprol), drugs against leprosy, cortisone and corticotropin (ACTH), antimalarial drugs, and dimenhydrinate (dramamine®). Obviously, the discussions are of necessity sketchy in most instances, but they are presented in a fairly unbiased fashion. A real attempt has been made to outline the shortcomings in the new methods of treatment, so that unjustified hopes will not be aroused.

In an era in which medical information is of such intense interest to the whole reading public, this book should be enthusiastically received.

Antibiotic Therapy. By Henry Welch, Ph.D., and Charles M. Lewis, M.D., with a foreword by Chester S. Keefer, M.D. Price, $10. Pp. 562, with many illustrations. Arundel Press, Inc., Box 2602, Washington 13, D. C., 1951.

This book is the best summary of the development and clinical usefulness of the various antibiotics which the reviewer has seen. All the commonly used antibiotics are discussed in detail, and a short evaluation of the newer ones not yet in use because of their toxicity or lack of sufficient clinical trial is made. The latter group includes polymyxin, neomycin, mycomycin, viomycin, and subtilin.

Discussions of the antibiotics begin with a short biography of the discoverers and an account of the steps leading to the development of each new potent antimicrobial agent. Then follows a discussion of the therapeutic usefulness and an account of the pharmacology, toxic reactions,

and forms of administrations of each drug. After all the antibiotics have been discussed, a final section of the book takes up their use, disease by disease. The truly enormous literature on the antibiotics has been adequately covered. At the end of each chapter is a long bibliography on the material covered.

Because both the laboratory studies and the clinical usefulness of each antibiotic have been so thoroughly covered, this book should be a welcome addition to the libraries of research workers, teachers, and clinicians.

A Dictionary of Antibiotics. Compiled by Leonard Karel, Ph.D., and Elizabeth Spencer Roach. Price, $8.50. Pp. 373. Columbia University Press, 2960 Broadway, New York 27, 1951.

The term antibiotic is defined in this book as a substance derived from living organisms and capable of adversely modifying the vital functions of specific organisms. The book is not a treatise on antibiosis, but a dictionary or encyclopedia. It provides in alphabetical order authoritative information on a great many substances with antibiotic activity. The source of the substance is named, the method of extraction, the chemical and physical properties, and, when available, the spectrum, structural formula, toxicological, pharmacological, and clinical properties. A very complete bibilography is included.

The principal author, Dr. Leonard Karel, is Executive Secretary of the Pharmacologic Section, Division of Research Grants, in the National Institutes of Health, United States Public Health Service. Mrs. Roach is his assistant.

The volume ought to be of very considerable usefulness to the specialist in pharmacology.

Urine and Urinary Sediment. By Richard W. Lippman, M.D. Price, $7.50. Pp. 124, with 61 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

This compact little volume is a remarkably interesting combination of the theory and practice of clinical urinalysis, with special emphasis on the interpretation of the urinary sediment. The general approach to the subject is that of the late Dr. Thomas Addis, whose guidance the author fortunately experienced.

The book comprises three sections—the first, on the significance of proteinuria and the elements of the urinary sediment; the second, on urinary findings in all types of renal disease, and the third, on details of technique. The text is clear and concise, and almost every page furnishes answers to questions that would arise in the mind of an intelligent medical student or physician. The bibliography is excellent.

The numerous illustrations in the form of color photographs of urinary sediments are virtually perfect. They have been carefully selected to show individual items and typical combinations found in specific renal diseases.

Two criticisms are in order: One is the omission of any reference to "motility cells," recently described by Sternheimer as characteristic for pyelonephritis with renal impairment. The other is the occasional failure of the author to distinguish clearly between fatty cells of the isotropic variety and those of the doubly refractile lipid type which have much more specific diagnostic significance. Anisotropic lipid is not found in the urine in heart failure without intrinsic renal disease.

Electroencephalography. By Robert S. Schwab, M.D. Price, $6.50. Pp. 195, with 106 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

This book should prove of value to those who wish to begin a study of electroencephalography. The author has simplified the problem. Many records are shown, and a brief discussion of the normal and abnormal patterns is presented. A bibliography follows each chapter, so that the reader may study original papers and other sources of information if he wishes. This book is recommended to those who wish to become acquainted with electroencephalography.

Conference on Adrenal Cortex: Transactions of the Second Conference, November 16-17, 1950, New York. Edited by Elaine P. Ralli. Price, $3. Pp. 209, with 68 illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

This small book is a mine of information on the timely subject of the adrenal cortex. It is a compilation of knowledge by a panel of eminent scientists and clinicians representing the breadth of the United States, as well as Canada. Five subdivisions, each introduced by a member especially qualified and then discussed by all members of the panel, provide the reader with easy access to his special field of interest. By this method, the lack of an index is not a great loss.

The subdivisions of the subject are as follows: (1) "The Present Status of the Chemistry of ACTH"; (2) "Regulation of Pituitary Adrenocorticotropic Activity"; (3) "The Relation of the Adrenal Cortical Hormones to the Hypersensitive State"; (4) "Hyaluronidase and the Adrenal Cortical Hormones," and (5) "Further Clinical Studies with ACTH and Adrenal Cortical Hormones." The last subdivision with its rationale for the management of the patient with Addison's disease makes the book well worth while for the clinician.

Easily deciphered charts and diagrams, glossy pages, and good format combine with the thread of the interesting question and answer method to make this book a valuable personal library item.

Conference on Blood Clotting and Allied Problems: Transactions of the Fourth Conference, Jan. 22-23, 1951, New York. Edited by Joseph E. Flynn, Department of Pathology, College of Physicians and Surgeons, Columbia University, New York. Price, $4. Pp. 272, with many illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

These transactions continue to afford a glimpse of the complexity of blood coagulation and allied problems. It seems that only through such informal discussion and frank criticism can part of this complex field be completely understood. As was true of previous volumes, this one is necessary to those interested in these problems.

Liver Disease: Proceedings of the Symposium Held in London Under the Auspices of the Ciba Foundation. Many contributors. Consulting editor, Sheila Sherlock, M.D., F.R.C.P. Price, $5. Pp. 249, with 112 illustrations and 35 tables. The Blakiston Company (Division of Doubleday & Company, Inc.), 1012 Walnut St., Philadelphia 5, 1951.

This book essentially is a bird's-eye view of problems in the physiology of hepatic disease. Many of the data presented have been published previously, and some of the most interesting parts of the book deal with the general discussion by those participating. It is not a book for the general practitioner but is useful solely to the student primarily interested in disease of the liver. The major criticism of the volume is that too large a field is covered in a small space.

The Practice of Endocrinology. Revised and enlarged edition. Edited by Raymond Greene, M.D., D.M., M.R.C.P. Price, $12.50. Pp. 416, with 53 plates. J. B. Lippincott Company, 227-231 S. 6th Ave., Philadelphia 5, 1951.

As is usual with most British textbooks, the clinical descriptions in this volume are well written, vivid, and adequate. The writer states in his preface that his book is intended for general practitioners "most of whom are too busy to concern themselves with unproven hypotheses and academic details." We are not sure that the implication of this statement—namely, that the general physician must be content with a sort of second-class knowledge—is sound. Actually many of the discussions, especially those of therapy, seem a little inadequate. Cortisone is not mentioned in the treatment of Addison's disease, although American physicians rely heavily on it. The discussion of the mechanism of diabetic acidosis is somewhat superficial, and the important role of potassium disturbance is lightly dismissed. Diet in diabetics is dealt with by referring to a table. The reasons for preparation of hyperthyroid patients for operation with thiouracil and iodine are not clearly analyzed. While there are many excellent features, that exact

precision of knowledge which is so important in modern practice seems somewhat lacking. The illustrations (some in color) and the charts are excellent and well selected, as are the references to the literature; on the whole, this is a readable and useful book.

Modern Dietary Treatment. Third edition. By Margery Abrahams, M.A. (Oxon.), M.Sc. (Columbia University), and Elsie M. Widdowson, D.Sc., Ph.D. (Lond.). Price, $4.50. Pp. 356, with many tables. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

This textbook should be of some help to dietitians, physicians, and nurses. It cannot be used easily by laymen. The material appears to be prepared for use intramurally in teaching and in the planning of special diets. The dietary programs are carefully planned, and the tables and charts represent detailed calculations.

The recipes might be of greater use if the amounts of ingredients in each recipe were given by household measures, as well as by weights. A table of the cholesterol content of food is not included, since the authors believe that cholesterol-free diets are of doubtful value. In general, it is a good book for use limited to the teaching of dietetics.

Conference on Problems of Aging: Transactions of the Thirteenth Conference. Edited by Nathan W. Shock. Price, $4. Pp. 194, with illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

Geriatrics is very much to the fore these days, and it is useful to have in print the deliberations of a group of experts. This volume deals with problems of aging as brought out in the conference held in February, 1951, and sponsored by the Josiah Macy, Jr., Foundation. Endocrine aspects, cardiovascular aspects, etc., are dealt with in considerable detail but in this particular symposium not much is taken up on the sociological, economic, or occupational side. The reviewer is not enthusiastic about the use of the Socratic dialogue in dealing with this material. There is much lost motion, and inconsequential things creep in, such as the following:

"Engle: Dr. Hamilton, may I interrupt, because Dr. Heilbrunn over here is getting very restless?

"Hamilton: I would like to hear what he has to say.

"Engle: You stay right up there because you have to defend yourself. Dr. Heilbrunn, you know all about nematodes."

Conference on Nerve Impulse: Transactions of the Second Conference. Edited by David Nachmansohn. Price, $3.50. Pp. 204, with tables and charts. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

This volume contains the material presented at one of the invaluable conferences sponsored by the Macy Foundation. The reviewer is not able to discuss with authority the technical side of this problem, which is highly complicated. However, current views in connection with nerve impulse are gone into with great thoroughness by experts, and the volume should be valuable to anyone working in the field.

Preventive Medicine and Hygiene. By Milton J. Rosenau. Seventh edition by K. F. Maxcy. Price, $14. Pp. 1462, with illustrations. Appleton-Century-Crofts Company, Inc., 35 W. 32d St., New York 1, 1951.

The first edition of this popular text was prepared by M. J. Rosenau in 1913. At that time public health was a new specialty which concerned itself largely with the prevention of communicable diseases. The wide field now encompassed by those engaged primarily in preventive medicine is illustrated by the great variety of subjects covered in the present volume, many of which were never considered the concern of public health physicians until recently. For instance, preventive medicine now encompasses nutrition, mental hygiene, occupational diseases, the effects of environmental factors, such as temperature, radiation, barometric pressure, and noise, on the population, and a variety of other conditions affecting community health.

Specific methods of disease prevention, prevention of food spoilage and contamination, and water purification are dealt with adequately. Dr. Maxcy assembled a group of distinguished collaborators, each a recognized authority on some phase of preventive medicine, to help in the preparation of this thoroughly up-to-date and useful volume. The book is a necessity for public health and industrial physicians. All internists should find parts of it of great value and interest.

Clinical Allergy: A Practical Guide to Diagnosis and Treatment. Second edition. By Samuel J. Taub, M.D. Price, $4.50. Pp. 276. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York 16, 1951.

The ARCHIVES approved of the first edition of this book (**77**:593 [May] 1946), characterizing it as a monograph written by a clinician familiar not only with allergy but also with medical students and practitioners. The book promised to fulfill the purpose for which it was prepared: to make the field of allergy easily accessible to beginners and to physicians who could not possibly read their way through the maze of literature on allergy.

The second edition follows the pattern of the first but is almost a hundred pages longer. It has been brought up to date, now includes discussion on the use of corticotropin (ACTH) and cortisone in the treatment of chronic intractable asthma, and discusses new concepts that may explain the part that allergy plays in migraine, periarteritis nodosa, and other conditions.

As was true of the first edition, the new edition is written intelligently; it will serve as a practical handbook for students and practitioners, and it deserves success.

Textbook of Clinical Neurology, with an Introduction to the History of Neurology. Seventh edition. By Israel S. Wechsler, M.D. Price, $9.50. Pp. 801, with 179 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1952.

The pattern and organization of this seventh edition of Wechsler's book are the same as those of previous editions. The preliminary sections cover history taking, physical examination and interpretation of physical findings, and psychological diagnosis. These sections are well written and instructive and contain much useful information, particularly for students and younger men in medicine. In the following sections, spinal cord, peripheral nerves, and brain are discussed completely. All diseases are well covered and are given their due amount of space as judged by their importance. The neuroses are discussed in a separate section. This section perhaps covers too much material rather briefly and is not too clearly written. The last section is a compact history of neurology. This is an excellent book, which is well indexed and contains adequate fundamental information.

The Musculoskeletal System. Edited by Mahlon Ashford, M.D., with many contributors. Price, $6.50. Pp. 368, with 103 illustrations. The Macmillan Company, 60 5th Ave., New York 11, 1952.

This neat volume includes a series of papers on the musculoskeletal system presented at the Twenty-Third Graduate Fortnight of the New York Academy of Medicine. The first papers deal with the structure and chemistry of connective tissue and with the physiology of muscle and of bone. The last half of the symposium is more concerned with clinical matters. The authors of the various papers are well known in their field and speak with authority; there are illustrations and lists of references. An index is lacking.

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			Duodenal	Jejunal	Stomal	Gastric	Good	Fair	Poor[1]	No Report			Complete	Moderate	None	No Report
Grimson, Lyons, Reeves	100	100	93	7			80	11	4		5		47		19	29
Friedman	15	15	14			1	5		4	6[3]			2			13
Bockgaard, Nielsen, Bang, Grunland, Tobiassen	26	26	21			5	16	4	6				8	6	12	
McHardy, Browne, Edwards, Marek, Ward	162		162				136	12	11		3	1	14	9	7	129
Segal, Friedman, Watson	34	34	34[4]				14	13			7	2	5		8	14
Brown, Collins	117	99	117				97	7	8		5	8	55	9	8	40
Acker	77		65		7	5	52	9	16			16		9	21	47
Rodriguez de la Vega, Reyes Diaz	5	4	5				4		1					3	2	
Winkelstein	116	116	102	8		6	102		14				53		18	45
Hall, Hornisher, Weeks	18	18	18				11		1	6[5]			18			
Miner, Meli	38	38	24			14[6]	27	7	4[7]				10	2	5	21
Meyer, Jarmin	25	18	25				21		4							25
Puth, Fromm	37	37	37				33	3	1				33	3	1	
Plummer, Burke, Williams	41	41	41				36		5				38		3	
McDonough, O'Neil	104	100	104				63	10	31			11	4		11	89
Broders	60	60	58		1	1	35	19	6				10	1	49[8]	
Legarton, Textor, Ruffin	11		11				11									11
Holoubek, Holoubek, Langford	76	69	76				35	27	10		4	10	26		10	36
Ogborn	42		39	2		1	42[9]									42
Shaiken	48	48	48				33	10	3		2		33	10	3	
Johnston	145	145	145				143		2			2	143		2	
Bossett, Knox, Stephenson	146		141			5	146					4[10]	53			93
TOTALS	1443	968	1390	17	8	38	1142	182	131	12	86	84	582	82	179	634
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1. Not included in tabulations.
2. Included in "Relief of Symptoms" as "Poor" and in "Evidence of Healing" as "None."
3. Four had no symptoms when Banthine therapy was begun.
4. Of which seven were penetrative lesions and five partially obstructive.
5. No symptoms were present in four.
6. Two with symptoms only; no demonstrable ulcer.
7. Three were psychopathic patients and one had a ventricular ulcer of the lesser curvature.
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10. In these four, after relief of symptoms, Banthine was discontinued because of urinary retention.

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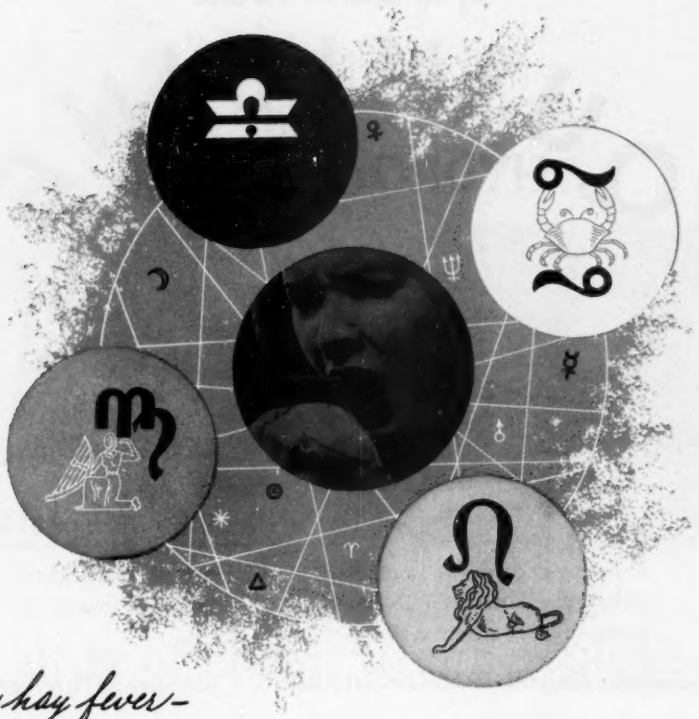

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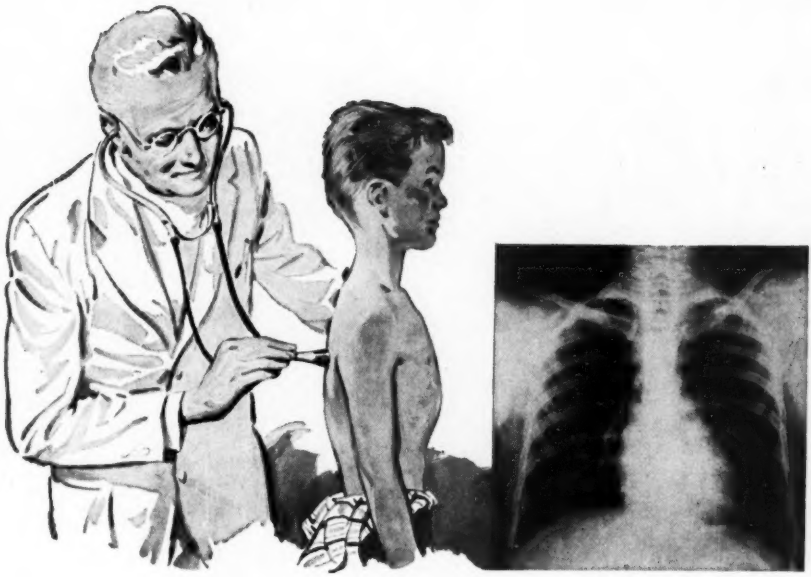

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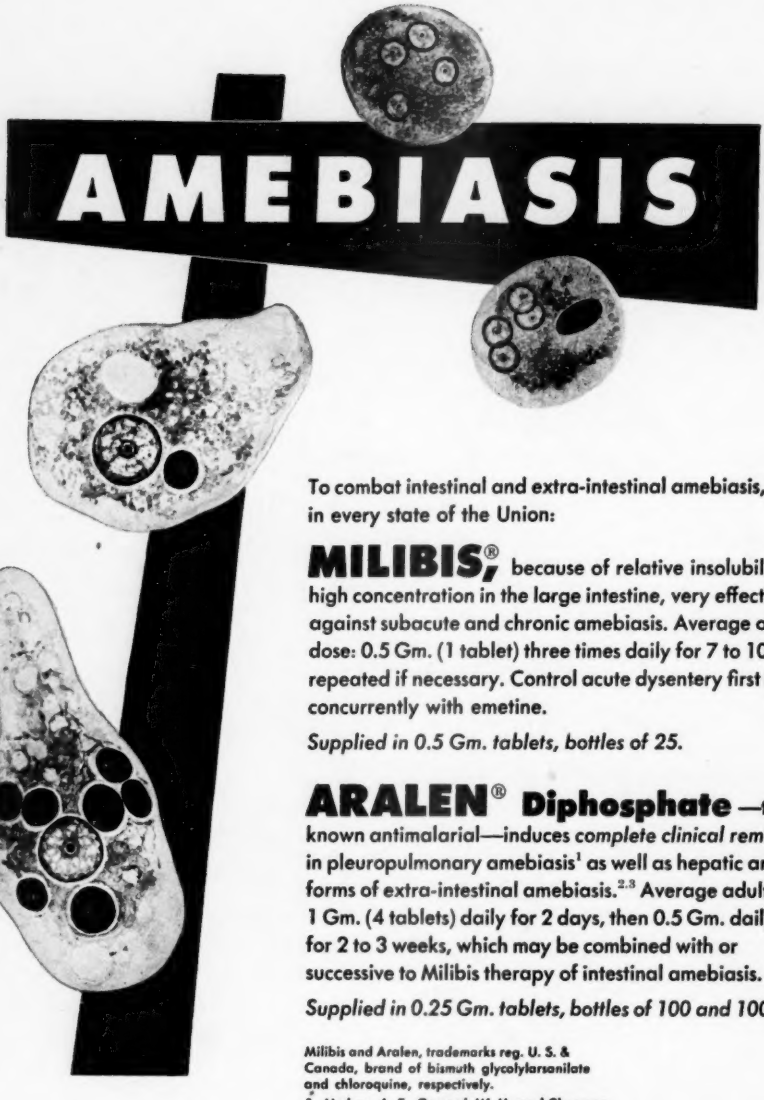

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